

Case Report

A case of chemotherapy induced hemolytic anemia of choriocarcinoma combined with hereditary spherocytosis

Yun Lin, Xueli Wei, Min Xue, Xinliang Deng, Xin Sun

Department of Obstetrics and Gynecology, The Third Xiangya Hospital of Central South University, Changsha 410013, Hunan, China

Received July 24, 2017; Accepted February 6, 2018; Epub March 15, 2018; Published March 30, 2018

Abstract: This study reported a case of hereditary spherocytosis patient presented hemolytic anemia during the chemotherapy of choriocarcinoma. A female patient aged 28 years old, gestation 5 times and pregnancy twice by cesarean section (G5P2), and admitted because of 5 months of postpartum vaginal bleeding. She was diagnosed as choriocarcinoma based on pathology and received uterine curettage. After surgery, she received etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA-CO) chemotherapy and resulted in severe anemia. Peripheral blood smear examination demonstrated a hereditary spherocytosis. EMA-CO chemotherapy was continued after blood transfusion, combined with γ -globulin intravenous injection, and prednisone treatment. Blood β -HCG did not decreased as expected, but elevated at the beginning of the third circle of chemotherapy, however, pelvic MRI presented unshrinking lesion. Thus, it was considered that EMA-CO resistance, and the patient underwent laparoscopy hysterectomy. Then she continued receiving EMA-CO chemotherapy postoperatively and the blood β -HCG back to normal. Comprehensive monitoring the state of illness is crucial for chemotherapy, which may induce severe complications. Rational and individualized treatment can improve the clinical effect and avoid drug resistance.

Keywords: Choriocarcinoma, hereditary spherocytosis, hemolytic anemia

Introduction

Choriocarcinoma is a rare disease with an extremely high malignancy in gestational trophoblastic tumor. It is featured as difficult treatment and poor prognosis [1-3]. Choriocarcinoma mainly occurs in women of childbearing age that can be secondary to hydatid mole, abortion, or full term birth. It is uncommon in unmarried women. The disease is easy to miss the best treatment opportunity because of missed diagnosis or misdiagnosis. Currently, chemotherapy is the mainstay of treatment, while the operation is supplemented. In the patients demand for children, the uterus should be preserved as much as possible or partial resection. When in a more severe condition, the ovary should be remained [4]. Choriocarcinoma is not difficult to metastasis, with the most common sites at lung, vagina, brain, and liver, which is the most familiar cause of death [5, 6].

Correct mastering the state of illness and coping strategy based on standard chemotherapy and individualized treatment is essential to improve the complete response rate, and reduce the recurrence and mortality in choriocarcinoma patients [7].

Hereditary spherocytosis (HS) is a chronic hemolytic disease caused by congenital erythrocyte membrane defects [8-10]. HS belongs to autosomal dominant inheritance that can be noted in both men and women. Changes on cell membrane protein is the main pathogenesis of HS, which is caused by erythrocyte membrane protein gene mutation and resulting in increasing red blood cell permeability, weakening deformation capacity, elevating brittleness, and eventually hemolytic anemia [9, 11]. Anemia, jaundice, hepatomegaly, and splenomegaly are its core clinical symptoms. Microspherocytes can reach 20-40% of the peripheral blood with

Chemotherapy induced hemolytic anemia of choriocarcinoma

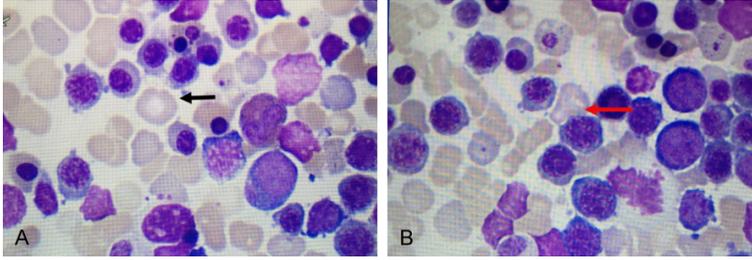


Figure 1. Microscopic peripheral blood smear (ocular 10× oil lens 100×). A. Wright staining, black arrow, normal erythrocytes in double concave disc type with central physiological light stained area. B. Red arrow, spherocytes in small round without central light stained area. The spherocytes accounted for 31% in the visual field.

significantly increased erythrocyte osmotic fragility [12, 13]. There is no relevant domestic epidemiological statistical information in China for its low incidence. The main treatment for HS is splenectomy which can cause many complications including infection, ischemic heart disease. However, cases of HS combined with choriocarcinoma are rarely reported. Thus, this study reported a case of hemolytic anemia induced by chemotherapy of choriocarcinoma combined with HS.

Materials and methods

Patient information

A female patient aged 28 years old, gestation 5 times and pregnancy twice by cesarean section (G5P2), and admitted because of 5 months of postpartum vaginal bleeding.

Treatment

The patient received 5-Fluorouracil+Kengshemycinl, (5-Fu+KSM) and etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA-CO) regimens for chemotherapy successively. She underwent laparoscopic hysterectomy later.

Results

Diagnosis of choriocarcinoma

The patient appeared irregular vaginal bleeding on 5 months after full-term normal delivery. Blood β -HCG was 147,000 mIU/mL. B-mode ultrasound showed a 38*32 mm irregular medium-high echo at the right uterine angle. The patient underwent uterine curettage and the pathology demonstrated endometrial hyperplasia-like changes with a small amount of

syncytiotrophoblast cells and intermediate trophoblast cells as well as excessive bleeding area. Blood β -HCG decreased to 80,121 mIU/mL on day 1, however, increased to 120,000 mIU/mL on day 7 after surgery. Based on above examination, the patient was diagnosed as choriocarcinoma (I: 8).

5-Fu+KSM regimen chemotherapy

The patient received two circles of 5-Fu+KSM chemotherapy and the blood β -HCG reduced to 3,000 mIU/mL. However, before the third circle of chemotherapy, the blood β -HCG increased to 58,677 mIU/mL, which was considered to be drug resistance.

EMA-CO regimen chemotherapy

Depending on above diagnosis, CT was employed to excluding pulmonary metastasis and the patient underwent EMA-CO regimen chemotherapy. Unfortunately, the patient appeared dizziness, fatigue, pale, jaundice, and dark urine on the third day of chemotherapy. Hemoglobin decreased from 85 g/L to 42 g/L, total bilirubin was 120.62 μ mol/L, and indirect bilirubin was 109.46 μ mol/L. Therefore, it was considered as acute hemolytic anemia. Hematology consultation suggested connective tissue examination, Coombs test, Mediterranean anemia screening and diagnosis experiments, and G-6-PD enzyme test. These results showed no abnormalities. However, Bone marrow cytology showed an active hyperplasia of erythroid cell. Then, the patient received blood transfusion, γ globulin intravenous injection, and prednisone treatment instead of continued chemotherapy.

Laparoscopic hysterectomy

The patient was diagnosed as HS for the peripheral blood smear showed spherical erythrocytosis accounted for 31% (Figure 1), while acute hemolysis was considered to be induced by chemotherapy drugs. Due to resistance to the 5-Fu+KSM regimen, the patient further underwent EMA-CO regimen chemotherapy under monitoring. The hemoglobin decreased to 50~70 g/L on the fourth day of each course

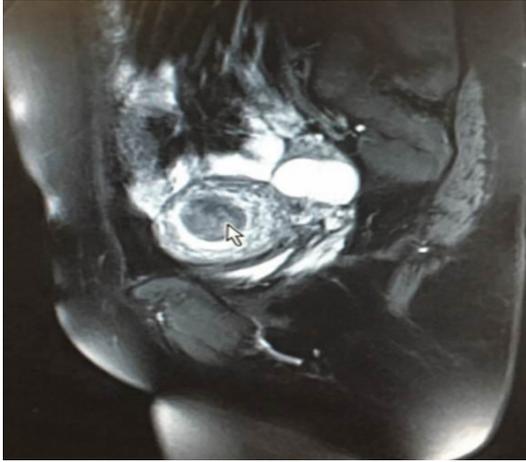


Figure 2. Pelvic MRI. Pelvic MRI showed a 3.5×3.2×3.0 cm signal in the right uterine angle with short T1 and shorter T2. The outer edge presented a long T2 signal loop with ring enhancement (arrow).



Figure 3. Postoperative specimen. A yellow mass (3.5*2.5*2cm) grew into the muscle layer infiltrating about 0.5 cm of the muscular wall. The thickness of muscular was 2 cm.

treatment of chemotherapy, thus the patient received 2-4 U concentrated erythrocytes transfusion. However, the blood β -HCG did not decrease after 3 courses of chemotherapy but with a slightly elevation. Pelvic MRI showed presented unshrunk lesion (**Figure 2**). Thus, it was considered that EMA-CO resistance. Thus, the patient underwent laparoscopic hysterectomy after the fourth course of chemotherapy for the patient had no fertility requirements. In the postoperative specimen examination, a light yellow toughness lesion at 1.5×2 cm was

found in the anterior muscle layer of the right uterine angle (**Figure 3**). Postoperative pathology showed that most of the lesion area was necrosis, with a small amount of heterotypic trophocyte nest infiltrating blood vessels and muscle wall with hemorrhagic necrosis (**Figure 4**). Then she continued receiving EMA-CO chemotherapy from the fourth day after surgery and the blood β -HCG back to normal on 1 month after surgery. The patient further underwent three courses of chemotherapy after three times of normal β -HCG. EMA-CO regimen was applied for 10 courses, and the patient was not relapse till now.

Discussion

Choriocarcinoma develops rapidly compared with other types of trophoblastic tumors. The initiation of effective chemotherapy decreased the mortality of choriocarcinoma effectively [14, 15]. Although the treatment effect has been greatly improved, chemotherapy-induced severe complications and resistance exhibited an important impact. HS is an autosomal dominant genetic disease mainly presented as anemia, jaundice, splenomegaly, significantly increased peripheral blood erythrocytes, augmented red blood cell osmotic fragility, and chronic anemia with acute hemolytic episode [16-18]. It often needs repeated blood transfusion treatment; however, it is rare to combine with choriocarcinoma. There is still lack of report about severe hemolytic anemia after chemotherapy. In addition, whether chemotherapy of choriocarcinoma affect HS remains unclear.

Diagnosis of HS combined choriocarcinoma

The patients in this case appeared abnormal postpartum vaginal bleeding and blood HCG elevation. She was diagnosed as choriocarcinoma based on imaging and pathological examination. She was suffered from an unclear history of anemia, but received no further examination. HS diagnostic criteria includes: 1) anemia, jaundice, splenomegaly as the characteristically clinical manifestations; 2) peripheral blood smear cells presented the proportion of spherocyte featured as small cell body, deep staining, and central light staining area disappear > 10%; 3) red blood cell osmotic fragility increase. Moreover, positive family history is helpful to confirm HS [9, 12, 19]. The spherical

Chemotherapy induced hemolytic anemia of choriocarcinoma

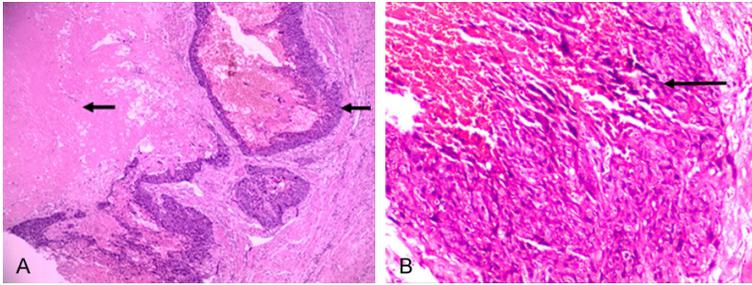


Figure 4. Pathological section. (A) HE staining showed necrosis in most lesion area (arrow) (100 \times). (B) Partially magnification for (A) HE staining exhibited a small amount of heterotypic trophocyte nest infiltrating blood vessels and muscle wall with hemorrhagic necrosis (black arrow, 400 \times).

erythrocytes of our patient were accounted for 31%, combined with anemia, splenomegaly, and cholecyst stone history. In addition, her son diagnosed as HS, thus she was confirmed as HS.

Etiological analysis of acute hemolytic anemia in HS combined choriocarcinoma chemotherapy

In general circumstances, the hemoglobin of HS patients can be maintained at about 90 g/L. Severe hemolytic anemia may be induced by infection or chemotherapy drugs. In this case, the patient did not appear hemolysis during 5-Fu+KSM chemotherapy, but acute severe hemolysis occurred in the first part of EMA-CO regimen. The first part of EMA-CO regimen contained actinomycin (dactinomycin, KSM), methotrexate (MTX), and etoposide (VP-16); and the second part contained vincristine (VCR) and cyclophosphamide (CTV). Since KSM exists in both of two regimens and no hemolysis appeared in the second part. Thus, KSM, VCR, and CTV were excluded to induce hemolysis. MTX is an anti-metabolic drug that can inhibit dihydrofolate reductase to prevent the tumor growth [20, 21]. There was no evidence that MTX can induce hemolysis. However, it was showed that VP-16 can induce hemolysis [22, 23]. Thus, we considered that acute hemolytic anemia in this patient was most likely induced by VP-16.

The treatment of HS combined by choriocarcinoma

There is no relevant report on HS combined by choriocarcinoma, thus clear treatment guide or experience couldn't be found. The 5-FU+KSM

or EMA-CO regimen was preferred for high-risk patients. In this study, the patient exhibited a resistance to 5-FU+KSM regimen and appeared hemolytic reaction in the first part of EMA-CO. Chemotherapy suspended by hemolysis has led the treatment lack of standardization. The commonly used second-line regimen for trophoblastic tumor including EMA-EP, TP-TE and BEP program, but both contained VP-16. Moreover, the efficiency of second-line regimen was only 30 to 40% [24].

There are no radical treatment measures for HS, though splenectomy can prevent spleen damage to the red blood cells, which may induce overwhelming postsplenectomy infection (OPSI). Furthermore, the incidence of OPSI was higher in hemolytic anemia patients after chemotherapy [12] and may lead to embolization [25]. Therefore, we continued EMA-CO regimen with closely monitoring hemoglobin and hemolytic symptoms. We adopted timely supportive treatment, such as blood transfusion, oral folic acid and vitamin E, and oral sodium bicarbonate to prevent the toxic effects caused by the destruction of a large number of red blood cells, including acute renal failure, shock, heart failure, kernicterus, hypoxic-ischemic encephalopathy, and hemolytic crisis. The patients underwent 10 cycles of EMA-CO regimen and appeared hemolysis each time. However, she did not appear severe side effects under active symptomatic support, suggesting that chemotherapy can be continued even with anemia with closely monitoring and symptomatic treatment to prevent the occurrence of complications.

Chemotherapy drug resistance in HS combined by choriocarcinoma

Although the cure rate of choriocarcinoma is increasing, there are still about 20% of patients are drug resistance [26]. Surgical treatment is an important method for the resistant lesions as it can reduce tumor load, shorten the course of chemotherapy, alleviate hemolysis, improve the cure rate of chemotherapy, and reduce recurrence [27, 28]. The patient appeared drug resistance after two circles of 5-Fu+KSM regimen and appeared drug resistance again in

Chemotherapy induced hemolytic anemia of choriocarcinoma

EMA-CO chemotherapy. She received laparoscopic hysterectomy and HCG decreased to normal after two courses of postoperative chemotherapy.

To sum up, HS combined with choriocarcinoma is rarely happen. Since there is no clear treatment program, it is important to fully assess the severity of HS and the potential side effects of chemotherapy. To prevent the occurrence of drug resistance, make the appropriate individual treatment would be effective strategies to achieve the best therapeutic effect.

Acknowledgments

This work was supported by the Planned Science and Technology Project of Hunan Province, China (NO.2012FJ4308).

Disclosure of conflict of interest

None.

Address correspondence to: Xin Sun, Department of Obstetrics and Gynecology, The Third Xiangya Hospital of Central South University, 138 Tongzipo Road, Yuelu District, Changsha 410013, Hunan, China. Tel: +86-0731-82151528; Fax: +86-0731-82151528; E-mail: xiangya_sunxin@163.com

References

- [1] Bratila E, Ionescu CA, Vladescu CT, Cirstoiu MM and Berceanu C. Gestational choriocarcinoma after term pregnancy: a case report. *Rom J Morphol Embryol* 2015; 56: 267-271.
- [2] Khan EM, Chakrabarti A and Dwary AD. Primary choriocarcinoma of appendix mimicking acute appendicitis. *J Cancer Res Ther* 2015; 11: 1031.
- [3] Mitrovic S, Arsenijevic PS, Kljakic D, Djuric JM, Milosavljevic MZ, Protrka ZM and Vojinovic RH. Gestational choriocarcinoma of the cervix. *Arch Iran Med* 2014; 17: 783-785.
- [4] Hanson D, Walter AW, Dunn S, Rittenhouse DW and Griffin G. Infantile choriocarcinoma in a neonate with massive liver involvement cured with chemotherapy and liver transplant. *J Pediatr Hematol Oncol* 2011; 33: e258-260.
- [5] Zhang W, Liu B, Wu J and Sun B. Hemoptysis as primary manifestation in three women with choriocarcinoma with pulmonary metastasis: a case series. *J Med Case Rep* 2017; 11: 110.
- [6] Kuno I, Matsumoto Y, Kasai M, Fukuda T, Hashiguchi Y, Ichimura T, Yasui T and Sumi T. Primary mediastinal choriocarcinoma with

- brain metastasis in a female patient. *Eur J Gynaecol Oncol* 2016; 37: 265-266.
- [7] Khurana RN, DiBernardo C and Handa JT. Improved systemic chemotherapy for metastatic testicular choriocarcinoma can result in excellent prognosis for life and vision. *Arch Ophthalmol* 2008; 126: 1008-1009.
- [8] Das A, Bansal D, Trehan A and Das R. Growth failure in hereditary spherocytosis and the effect of splenectomy. *Indian Pediatr* 2017; 54: 563-566.
- [9] Farias MG. Advances in laboratory diagnosis of hereditary spherocytosis. *Clin Chem Lab Med* 2017; 55: 944-948.
- [10] Tao YF, Deng ZF, Liao L, Qiu YL, Deng XL, Chen WQ and Lin FQ. Evaluation of a flow-cytometric osmotic fragility test for hereditary spherocytosis in chinese patients. *Acta Haematol* 2016; 135: 88-93.
- [11] Langeveld TJC, van Rossum AP, van der Zwaag B, van Wijk R and Vlasveld LT. Profound spherocytosis in adulthood: acquired, hereditary or both? *Int J Lab Hematol* 2017; 39: e117-e120.
- [12] Manciu S, Matei E and Trandafir B. Hereditary spherocytosis-diagnosis, surgical treatment and outcomes. A literature review. *Chirurgia (Bucur)* 2017; 112: 110-116.
- [13] Buesing KL, Tracy ET, Kiernan C, Pastor AC, Cassidy LD, Scott JP, Ware RE, Davidoff AM, Rescorla FJ, Langer JC, Rice HE and Oldham KT. Partial splenectomy for hereditary spherocytosis: a multi-institutional review. *J Pediatr Surg* 2011; 46: 178-183.
- [14] Ramessur A, Openshaw M and Sarwar N. Intussusception in gestational choriocarcinoma (not histologically proven), resolving spontaneously with chemotherapy. *BMJ Case Rep* 2015; 2015.
- [15] Bhonsale A and Fonseca M. Successful pregnancy after chemotherapy for choriocarcinoma. *J Obstet Gynaecol India* 2012; 62: 197-198.
- [16] Konca C, Soker M, Tas MA and Yildirim R. Hereditary spherocytosis: evaluation of 68 children. *Indian J Hematol Blood Transfus* 2015; 31: 127-132.
- [17] Das A, Bansal D, Das R, Trehan A and Marwaha RK. Hereditary spherocytosis in children: profile and post-splenectomy outcome. *Indian Pediatr* 2014; 51: 139-141.
- [18] Polat A, Ozgurur F, Balci YI, Kocyigit A and Tan M. Hereditary spherocytosis and wandering spleen. *Pediatr Hematol Oncol* 2014; 31: 101-103.
- [19] Bianchi P, Fermo E, Vercellati C, Marcello AP, Porretti L, Cortelezzi A, Barcellini W and Zanello A. Diagnostic power of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecu-

Chemotherapy induced hemolytic anemia of choriocarcinoma

- lar and clinical characteristics. *Haematologica* 2012; 97: 516-523.
- [20] Cipolleschi MG, Marzi I, Rovida E, Olivotto M and Dello Sbarba P. Low-dose methotrexate enhances cycling of highly anaplastic cancer cells. *Cell Cycle* 2017; 16: 280-285.
- [21] Yan KH, Lee LM, Hsieh MC, Yan MD, Yao CJ, Chang PY, Chen TL, Chang HY, Cheng AL, Lai GM and Chuang SE. Aspirin antagonizes the cytotoxic effect of methotrexate in lung cancer cells. *Oncol Rep* 2013; 30: 1497-1505.
- [22] Heger Z, Polanska H, Krizkova S, Balvan J, Raudenska M, Dostalova S, Moulick A, Masarik M and Adam V. Co-delivery of VP-16 and Bcl-2-targeted antisense on PEG-grafted oMW-CNTs for synergistic in vitro anti-cancer effects in non-small and small cell lung cancer. *Colloids Surf B Biointerfaces* 2017; 150: 131-140.
- [23] Ukawala M, Rajyaguru T, Chaudhari K, Manjappa AS, Pimple S, Babbar AK, Mathur R, Mishra AK and Murthy RS. Investigation on design of stable etoposide-loaded PEG-PCL micelles: effect of molecular weight of PEG-PCL diblock copolymer on the in vitro and in vivo performance of micelles. *Drug Deliv* 2012; 19: 155-167.
- [24] Essel KG, Bruegl A, Gershenson DM, Ramondetta LM, Naumann RW and Brown J. Salvage chemotherapy for gestational trophoblastic neoplasia: utility or futility? *Gynecol Oncol* 2017; 146: 74-80.
- [25] Troendle SB, Adix L, Crary SE and Buchanan GR. Laboratory markers of thrombosis risk in children with hereditary spherocytosis. *Pediatr Blood Cancer* 2007; 49: 781-785.
- [26] Alazzam M, Tidy J, Osborne R, Coleman R, Hancock BW and Lawrie TA. Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. *Cochrane Database Syst Rev* 2012; 12: CD008891.
- [27] Ba MC, Long H and Wu YB. Treatment of gestational choriocarcinoma and massive ascites by hypothermic intraperitoneal perfusion chemotherapy guided by ultrasound followed by cytoreductive surgery. *Pak J Med Sci* 2013; 29: 663-665.
- [28] Jeremic K, Gojnic M, Boskovic V, Argirovic R, Milenkovic V and Jeremic J. Treatment of choriocarcinoma metastases by surgery and polychemotherapy - case report. *Eur J Gynaecol Oncol* 2006; 27: 162-164.