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Chemotherapy-induced hemolytic uremic syndrome in locally advanced cervical cancer treated with combination chemotherapy after laparoscopic radical hysterectomy: a case report and review of the literature

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Summary

Hemolytic uremic syndrome (HUS) is a rare complication of chemotherapy characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure without disseminated intravascular coagulation. Although few cases of chemotherapy-induced HUS have been reported in gynecologic malignancy, it can be a fulminant, chronic disease and can be managed with early aggressive treatment. A 38-year-old woman was diagnosed with FIGO Stage IIb squamous cell carcinoma of the uterine cervix. After three cycles of neoadjuvant chemotherapy that consisted of a combined regimen of mytomicin-C, vincristine, and cisplatin, a laparoscopic radical hysterectomy was performed, and the pathological diagnosis of the residual lesion was deep stromal invasion. Following two adjuvant courses of the same chemotherapy, she developed chemotherapy-induced HUS. The patient was aggressively treated with therapeutic plasma exchange with fresh-frozen plasma and a high dose of steroids. At the last follow-up, the serum creatinine level had decreased to 1.81 mg/dl, and evidence of recurrence was not found.

Key words: Hemolytic uremic syndrome; Mitomycin-C; Neoadjuvant chemotherapy; Therapeutic plasma exchange; Cervical cancer.

Introduction

Hemolytic uremic syndrome (HUS) is a rare complication of chemotherapy characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure without disseminated intravascular coagulation. The presentation of HUS includes hypertension and peripheral edema that proceeds to severe pulmonary edema and respiratory distress [1, 2]. This syndrome occurs in 2-10% of cancer patients who receive chemotherapy, most often with mitomycin-C. Other chemotherapeutic agents, such as bleomycin, cisplatin, carboplatin, doxorubicin, and gemcitabine, have also been implicated in causing HUS [3]. The diagnosis of chemotherapy-induced HUS (C-HUS) is often delayed, because most chemotherapeutic agents are nephrotoxic and hematologically toxic and can cause non-specific anemia and thrombocytopenia. Early recognition and treatment is important because the mortality rate of C-HUS is high (ranges from 50% to 70%) [4]. Many methods have been employed in an attempt to treat HUS, such as steroids, therapeutic plasma exchange (TPE) with fresh-frozen plasma, aspirin, and heparin. The effect of steroids and antiplatelet agents has not been sufficiently demonstrated [5]. Although TPE elicited some response and normalized the hematologic abnormalities, renal impairment was rarely reversed [6, 7]. The authors report a case of C-HUS in a locally advanced cervical cancer patient receiving neoadjuvant and adjuvant combination chemotherapy after laparoscopic radical hysterectomy.

Case Report

A 38-year-old woman, gravida 2, para 2, was diagnosed with locally advanced FIGO Stage IIb invasive squamous cell cancer of the uterine cervix in June 2012. A pelvic examination indicated a 4.5×3 cm-sized exophytic mass invading the entire cervix with left side parametrial involvement. The serum squamous cell cancer antigen (SCC-Ag) level was elevated to 3.6 ng/ml. From July to August 2012, the patient underwent three cycles of neoadjuvant chemotherapy that consisted of a combined regimen of mytomicin-C (ten mg/m^2), vincristine (one mg/m^2) and cisplatin (75 mg/m^2) at three-week intervals. After three cycles of neoadjuvant chemotherapy, MRI indicated that the patient was free of remnant cancerous lesions. Two weeks later after the third cycle of chemotherapy, she received a laparoscopic radical hysterectomy with pelvic and para-aortic lymphadenectomy. On the pathologic report, the residual tumor was sized 1.3×1.2×0.7 cm in the cervix with deep stromal invasion. Neither lymph-vascular involvement nor parametrial infiltration were found. From October 2012 to November 2012, she received two cycles of adjuvant postoperative chemotherapy in the

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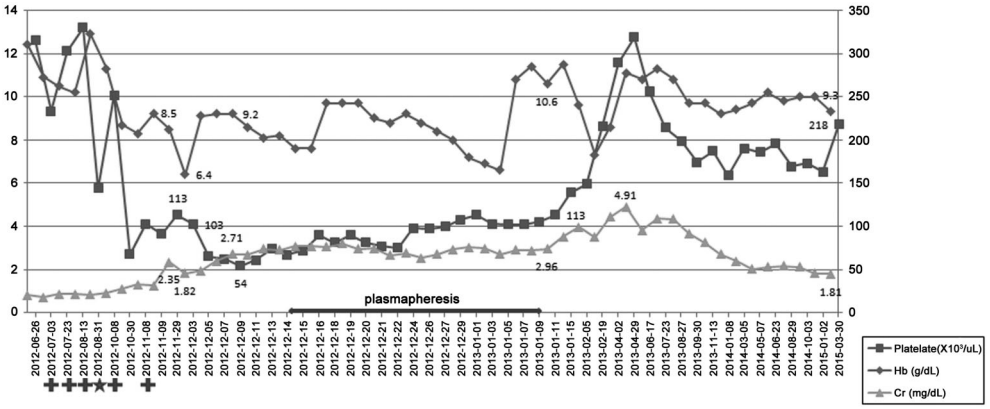

Figure 1. — Laboratory data of a woman with locally advanced cervical cancer who developed HUS after receiving combination chemotherapy. Cr, creatinine; Hb, hemoglobin; Cross, the date of chemotherapy; Star, the date of laparoscopic radical hysterectomy; Arrow, the period of therapeutic plasma exchange (TPE).

same manner. In total, five chemotherapy cycles were performed, including three neoadjuvant cycles and two adjuvant cycles after surgery. Chemotherapy was delayed by ten days because of thrombocytopenia between the fourth and fifth cycles, but her platelet count spontaneously recovered. When she was admitted for the sixth cycle of chemotherapy, the serum blood urea nitrogen (BUN) level was elevated to 34.8 mg/dl, and the serum creatinine (Cr) level was 2.35 mg/dl. Her hemoglobin (Hb) level had dropped from 8.5 g/dl to 6.4 g/dl within three days. She received a blood transfusion, but she presented with dyspnea with pitting edema of legs a few days later. Shortness of breath and peripheral edema were improved after the administration of diuretics. However, at that time (ten days after admission for the sixth cycle of chemotherapy), her Cr level had increased to 2.71 mg/dl, the platelet count decreased to $5.4\times10^3/\mu L$ and the Hb level decreased to 9.2 mg/dl. Additional laboratory tests were conducted to discriminate the thrombotic microangiopathy. A peripheral blood smear demonstrated many fragmented erythrocytes. The reticulocyte count was elevated (2.45%), the serum lactate dehydrogenase (LDH) level was elevated (762 IU/L), the haptoglobin level was low (two mg/dl), and direct Coombs' test was negative. A mild elevation of D-dimer with normal fibrinogen level suggested that these changes were not due to disseminated intravascular coagulation. The laboratory results confirmed the diagnosis of HUS. The authors promptly started TPE with fresh-frozen plasma replacement every other day as well as high-dose steroid therapy (prednisolone 50 mg/day). The patient received 11 TPEs over one month. The patient was regularly followed in an outpatient clinic, and the steroids were tapered off. Her laboratory parameters slowly improved over one month. In January 2013, her Hb level was 10.6 g/dl, platelet count was 113 $\times10^3/\mu L$ and LDH level was 616 IU/L, despite a persistently high Cr level (2.96 mg/dl). High blood pressure and renal function had been controlled by medication, including a calcium channel blocker, angiotensin converting enzyme inhibitor, and diuretics. The Cr level had been continuously elevated at 4.91 mg/dl in April 2013, and the authors planned to prepare for hemodialysis. However, her Cr since then decreased without hemodialysis. At the latest follow-up in March 2015, her Cr level was 1.81 mg/dl (Figure 1). Cervical cancer surveillance did not produce evidence of disease recurrence.

Discussion

The standard treatment of uterine cervical cancer has consisted in radical hysterectomy with lymph node dissection or cisplatin-based chemoradiation therapy [8]. Traditionally, systemic chemotherapy has been limited to cervical cancer with distant metastasis. The survival rates of women with locally advanced cervical cancer, which is a tumor larger than four cm, is poor, as low as 50-60%. To improve the therapeutic result, an alternative approach of neoadjuvant chemotherapy followed by surgery has been considered. Chemotherapy-induced HUS (C-HUS), which occurs during the treatment of gynecologic malignancies, is very rare, and only two cases have been reported in cervical cancer (Table 1) [9].

Chemotherapeutic agents that have been reported to be associated with C-HUS include bleomycin, cyclosporine, cisplatin, fluorouracil, and fludarabine, gemcitabine, and doxorubicin. The most commonly reported agent is mytomicin-C, whose use is associated with an incidence rate of 2-10% [2]. In the present case, the chemotherapeutic agents administered were mitomycin-C, vincristine, and cisplatin. The authors cannot be sure of the agent that caused C-HUS. All three agents can cause HUS; however, mitomycin-C is the agent most frequently associated with C-HUS. As shown in previous reports, a total cumulative dose of mitomycin-C above 30 mg/m^2 induces HUS [10]. The total cumulative dose of mitomycin C might be more important to consider than the dose per cycle or the number of cycles [1]. In the present case, the woman was administered a total dose of 50 mg/m^2 of mitomycin-C. Usually, mitomycin-C-induced HUS occurs four to eight weeks after the last cycle of chemotherapy but sometimes starts immediately after therapy or after eight months [11]. The authors diagnosed HUS after five weeks at the start of the fifth cycle of chemotherapy. This timing is almost the same as that given in previous reports.

Cisplatin is also known to cause HUS, but the incidence

Table 1. — *Cases of chemotherapy-induced HUS in gynecologic malignancies.*

Case	Reference	Age	Cancer site/ Cell type/ FIGO stage	Primary cancer treatment	Chemotherapy; Regimen x cycles	Platelet count ($x10^3$/ul); Peak creatinine (mg/dl)	Chemo-induced HUS treatment	Dialysis	Outcome
1	Van der Meer J et al., *J cancer Res Clin Oncol* 1985;110:119-122	23	Ovary/ Sertoli-Leydig cell tumor/ NA	Surgery	Adjuvant VBP x NA	NA	FFP, aspirin, dipyridamole	No	Expired of pneumonia
2	Angiola G et al., *Gynecol Oncol* 1990;39: 214-217	58	Cervix/ SCCa/ IVa	Whole-pelvis RT	Neoadjuvant VBP x 3	32; 6.5	Steroids, aspirin dipyridamole	Yes	Hematologic improvement, persistent renal insufficiency
3	Gross M et al., *Anticancer Drugs* 1999;10:533-536	50	Ovary/ NA/ NA	Surgery	Adjuvant; GC x 9	22; 2.05	TPE	NA	Recovered from HUS
4	V Tsatsaris et al., *Rev Med Interne* 1996;17;749-753	45	Uterus/ leomyosarcoma/ III	Surgery - Hysterectomy	Adjuvant V+ Actinomycin D	98; NA	Steroid TPE	No	Expired of HUS, renal and pulmonary failure
5	Walter RB et al., *Am J Kidney Dis* 2002;40:E16	45	Ovary/ adenocarcinoma/ IIIc	Surgery	Adjuvant G x 7, G x 2	69; NA	None	No	Improved HUS; Expired of cancer
6	Karim M et al., *Clin Nephrol* 2002;58:384-388	59	Ovary/ NA/ IIb	Surgery	Adjuvant Monthly C x 5	69; 6.34	TPE	Yes	Expired, final postmortem diagnosis-systemic sclerosis, not HUS
7	Ogunleye DA et al., *Obstet Gynecol* 2004;104:1184-1187	34	Ovary/ EST Ic	Surgery - Left salpingo-oophorectomy	Adjuvant; BEP x 3	88; 5.2	TPE	Yes	Recovered from HUS
8	Lewin SN et al., *Gynecol Oncol* 2005;97:228-233	57	Ovary/ PSAC/ IIIc	Surgery - Cytoreductive operation	Adjuvant; G/PLD x 6	25; 3.6	TPE	No	Expired of HUS, aggravated renal failure and diffuse lung injury
9	Lewin SN et al., *Gynecol Oncol* 2005;97:228-233	57	Ovary/ PSAC/ IIIc	Surgery - Cytoreductive operation	Adjuvant; G/PLD x 7	20; 3.2	Symptomatic treatment	No	Hematologic improvement, persistent renal insufficiency
10	Lewin SN et al., *Gyneco Oncol* 2005;97:228-233	57	Ovary/ PSAC/ IIIc	Surgery - Cytoreductive operation	Adjuvant; G/PLD x 5	NA; 3.6	None	No	Expired of cancer
11	Chopin N et al., *Gynecol Oncol* 2006;101:549-550	46	Ovary/ NA/ IV	Surgery - Cytoreductive operation	Adjuvant; GC x 9	NA; NA	Dalteparin	No	Recovered from HUS
12	Kalra N et al., *Int J ClnOncol* 2007;12: 38507	48	Ovary/ NA/ IIIc	Surgery - Cytoreductive operation	Adjuvant; G x 4	49; 5.2	TPE	Yes	Hematologic improvement, persistent renal insufficiency
13	Current case	36	Cervix/ SCCa/ IIb	Surgery - LRH	Neoadjuvant; MVP x 3 Adjuvant MVP x 2	54; 4.91	TPE	No	Hematologic improvement, persistent renal insufficiency

B, bleomycin; C, carboplatin; D, docetaxel; E, Etoposide; H, Topotecan; G, gemcitabine; M, mitomycin-c; P, cisplatin; T, paclitaxel; V, vincristine; PLD, pegylated doxorubicin. EST, endodermal sinus tumor; FFP, fresh frozen plasma; HUS, hemolytic uremic syndrome; LRH, laparoscopic radical hysterectomy; NA, not available; PSAC, papillary serous adenocarcinoma; RT, radiation therapy; SCCa, squamous cell carcinoma; TPE, therapeutic plasma exchange.

of cisplatin-associated HUS is lower than that of mitomycin-C-associated HUS. As reported in the literature, patients who receive long regimens of platinum-based chemotherapy are likely to progress to HUS [12]. The standard schedule of platinum-based agents consists of six cycles. In this case, the patient received five cycles of chemotherapy, which was less than the usual amount. Based on the above information, C-HUS was more likely to be caused by mitomycin-C rather than by cisplatin.

The diagnosis of C-HUS is difficult and often delayed, because chemotherapeutic agents such as mitomycin-C and cisplatin that are nephrotoxic and hematologically

toxic also cause non-specific anemia and thrombocytopenia. Thrombotic microangiopathy is relatively rare, its incidence rate is less than 1%, but its mortality is high, nearly 75% despite extensive therapy [11].

The authors reviewed 13 cases of C-HUS that appeared in gynecologic cancer. Of the seven living patients, only three patients have fully recovered from C-HUS, and the other four patients recovered from thrombocytopenia and anemia, but continue to suffer from chronic renal insufficiency. Hematologic improvement is common, but renal impairment is not fully reversible in most patients. Of the six patients that died, three patients died of renal failure or pulmonary failure caused by C-HUS, two patients died due to gynecologic malignancy, and the last patient died because of the progression of underlying systemic sclerosis (Table 1). Although few cases of chemotherapy-induced HUS have been reported in gynecologic malignancy, C-HUS should not be neglected, because its mortality rate is as high as that of gynecologic cancer. Gynecologic oncologists should consider the possibility of thrombotic microangiopathy when using drugs that are known to significantly increase the risk of C-HUS. Decreased renal function with anemia and thrombocytopenia is a sign of thrombotic microangiopathy. The clinical syndrome combines peripheral edema and hypertension, eventually leading to adult respiratory distress syndrome and non-cardiologic pulmonary edema [1]. Blood transfusion sometimes worsens the symptoms of C-HUS because of a risk for pulmonary adverse reactions; therefore, blood transfusions need to be carefully observed. Early detection of microangiopathy and prompt treatment, such as TPE and high-dose steroids, are most important for the improvement of prognosis.

In conclusion, in establishing a treatment plan for gynecologic malignancy, gynecologic oncologists should be aware of not only the course of malignancy itself, but also other factors that can affect subsequent survival and prognosis, including the complications of chemotherapy. Although reports of C-HUS in gynecologic malignancy have been rare, the syndrome can be fatal and cause fulminant disease and chronic renal insufficiency. The frequent monitoring of renal function and close observation of the patient are essential during chemotherapy for gynecologic malignancy.

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