



Case report

Advanced ovarian cancer that resulted in death from intestinal perforation following tumor lysis syndrome: A case report

Saki Kunimoto^{*,1}, Lena Tashima², Kimihiko Ito, Kensuke Hori

Department of Obstetrics & Gynecology, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki City, Hyogo 660-8511, Japan

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ABSTRACT

Introduction and importance: Tumor lysis syndrome (TLS) is an oncologic emergency, with 20 % cases occurring in solid tumors. Preventive measures are necessary depending on TLS risk. We report a case of TLS development after chemotherapy for advanced ovarian cancer which resulted in death by intestinal perforation.

Case presentation: A 76-year-old woman with multiple metastases had multi-cystic mass in the pelvic cavity. We diagnosed stage IVB ovarian cancer after exploratory laparoscopy and imaging test. Paclitaxel and carboplatin were started as neoadjuvant chemotherapy. Since day 4 of chemotherapy, vomiting, appetite loss, and diarrhea manifested; blood tests on day 9 showed electrolyte abnormality and decreased renal function. We diagnosed TLS and ileus. Her symptoms disappeared and blood chemistry improved after electrolyte correction in intensive care unit. However, vomiting and arrhythmia worsened on day 11, consciousness level lowered, and computed tomography showed intestinal perforation. She died on day 13.

Clinical discussion: Advanced ovarian cancer is at high TLS risk due to large tumors, multiple metastases, and impaired renal function caused by urinary tract stenosis. TLS reported in ovarian cancer had large tumor volume; disease onset was often within 1 week after chemotherapy. After TLS improves, follow-up is necessary to detect serious complications. In ovarian cancer with intestinal adhesions, intestinal perforation risk should be considered, and intestinal wall invasion may be evaluated before treatment.

Conclusion: TLS can be followed by fatal complications; many advanced ovarian cancers are at high TLS risk. Therefore, prophylactic measures and adequate information to patients and families before chemotherapy are necessary.

1. Introduction and importance

Tumor lysis syndrome (TLS) is an oncologic emergency caused by rapidly released cellular metabolites, such as nucleic acids, proteins, phosphorus, and potassium, as tumor cells collapse due to chemotherapy. Since its first report in the 1970s, the general features and treatment strategy of TLS are widely recognized by oncologists; however, the prophylactic aspect and complication management need considerable improvement. TLS is associated with hematologic malignancies, and although rare in solid tumors, 20 % cases occur in solid tumors [1]. Fortunately, TLS in solid tumors is sometimes predictable, so preventive measures should be taken depending on TLS risk, such as tumor size and chemosensitivity.

Here, we report a case of TLS development after the first

chemotherapy round for advanced ovarian cancer which resulted in death by intestinal perforation shortly after recovery from TLS, in line with the SCARE 2020 criteria [2].

2. Case presentation

A 76-year-old woman was referred to our hospital for primary unknown adenocarcinoma. There was nothing noteworthy about her internal medication history, family history or social background. Magnetic resonance imaging and computed tomography (CT) revealed a 10 × 7-cm multi-cystic mass with the solid part in the left side of the pelvic cavity, ascites, thickened omentum, extensive peritoneal dissemination, and multiple metastases to the spleen and liver in addition to pleural effusion (Fig. 1). Cancer antigen-125 and human epididymis protein 4

* Corresponding author at: Department of Obstetrics & Gynecology, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki City, Hyogo 660-8511, Japan.
E-mail address: u033400j@gmail.com (S. Kunimoto).

¹ Moved to Department of Obstetrics & Gynecology, Hyogo Prefectural Nishinomiya Hospital, 13-9 Rokutanjicho Nishinomiya city, Hyogo, JAPAN, 662-0918.

² Moved to Department of Gynecology, Osaka Kaisei Hospital, 1-6-10 Miyahara Yodogawaku Osaka city, JAPAN, 532-0003.

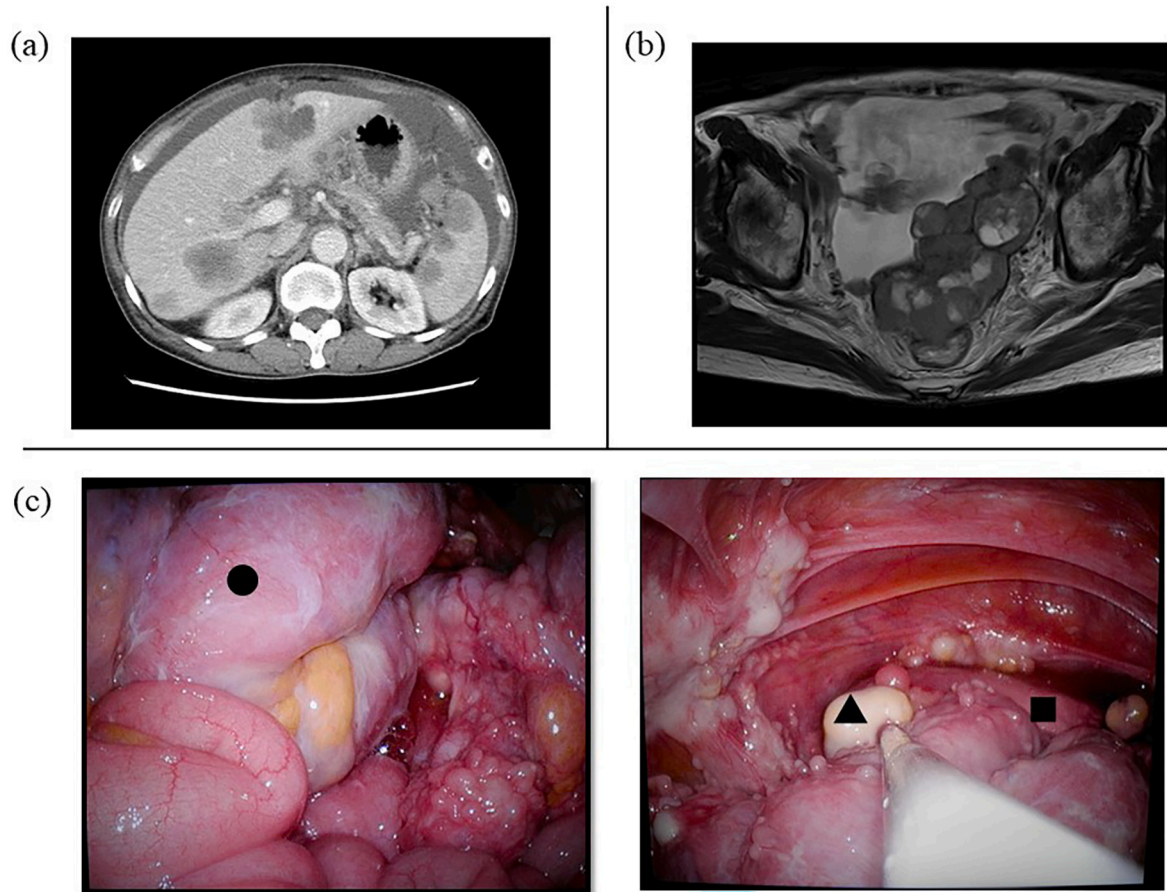


Fig. 1. Computed tomography (CT), magnetic resonance imaging (MRI), and laparoscopic findings.

(a). CT shows multiple metastases to the other organs.

(b). MRI (T2-weighted imaging) shows the left adnexa surrounded by the intestine; dissemination was highly suspected.

(c). Exploratory laparoscopy. Massive dissemination covered all over the peritoneal cavity.

● = sigmoid colon ▲ = dissemination ■ = uterus.

levels increased to 91.8 U/mL and 888 pmol/L, respectively. Carbohydrate antigen 19-9 was normal at 6.5 U/mL. Based on these findings, suspecting a primary malignancy of the left ovary, we performed an exploratory laparoscopy.

Ascites volume was 1.6 L. The left ovary had adhered tightly to the sigmoid colon, so the left adnexal lesion could not be completely visualized. Despite normal uterus, there was marked dissemination in the vesicouterine pouch, and the right ovary was mildly enlarged. Numerous disseminated lesions were found on the intestinal surface, peritoneum, omentum, diaphragm, and liver surface. A part of the peritoneal disseminated lesion was biopsied, and histopathological diagnosis of high-grade serous carcinoma was obtained. We diagnosed stage IVB ovarian cancer from laparoscopic and imaging findings.

Due to extensive peritoneal dissemination and multiple organ metastases, dose-dense paclitaxel-carboplatin (TC: weekly paclitaxel, 80 mg/m²; carboplatin, area under the curve [AUC] 5 on day 1) was initiated as neoadjuvant chemotherapy. She and her family agreed to this course of treatment. We followed our protocol, which stipulates that the first administration of TC requires hospitalization. The patient's general condition after day 1 of chemotherapy was good. She was

therefore discharged the next day. She had symptoms of vomiting, appetite loss, and diarrhea since day 4; however, she and her family considered them as side effects of chemotherapy and decided to wait at home. However, on day 9, during the first appointment after chemotherapy, her symptoms worsened, and she became bed-ridden due to fatigue. Blood tests showed electrolyte abnormality and decreased renal function: uric acid 9.9 mg/dL, potassium 5.3 mmol/dL, phosphate 9.5 mg/dL, and creatinine 2.22 mg/dL. Electrocardiography showed premature ventricular contractions, and abdominal radiography revealed multiple air-fluid levels; therefore, the diagnosis of TLS and ileus was confirmed. We admitted her to the intensive care unit (ICU) and started immediate treatment with febusostat, saline hydration, and calcium gluconate. Her symptoms of nausea and palpitation disappeared soon after treatment, and her blood chemistry and arrhythmia improved. She was moved from the ICU to the general ward on day 11. However, vomiting and arrhythmia reappeared at night in the absence of abnormal blood chemistry. Her consciousness level decreased the next morning. Free air was found in the abdominal cavity on non-contrast CT. Intestinal perforation was therefore assumed. Although the exact site of perforation was difficult to identify on imaging, the area of adhesion



Fig. 2. Plain abdominal radiography on day 9. Abdominal radiography revealed multiple air-fluid levels.

between the left ovarian tumor and sigmoid colon was most suspected (Fig. 2).

Perforation repair surgery was considered a treatment option; however, it was deemed impossible due to massive dissemination to the intestine and due to the patient's poor condition. The likely outcomes of surgery and of simple observation without surgery were explained to her family. Palliative intraperitoneal drainage was another option, although this would only prolong her life by a few days or cause death during the operation.

We suggested best supportive care (BSC), which provides symptom relief without active treatment. We also informed the family that her

general condition was extremely poor, and she may die within a day. Neither operation nor BSC was easily acceptable for her family. They finally decided against active treatment, which would distress her. The patient died the next day (Fig. 3).

3. Clinical discussion

Solid tumors are less associated with TLS than hematologic tumors. However, TLS risk in solid tumors has increased in recent years because effective drugs and regimens including molecularly targeted agents have been increasingly used [3]. Gynecologic tumors are not an exception.

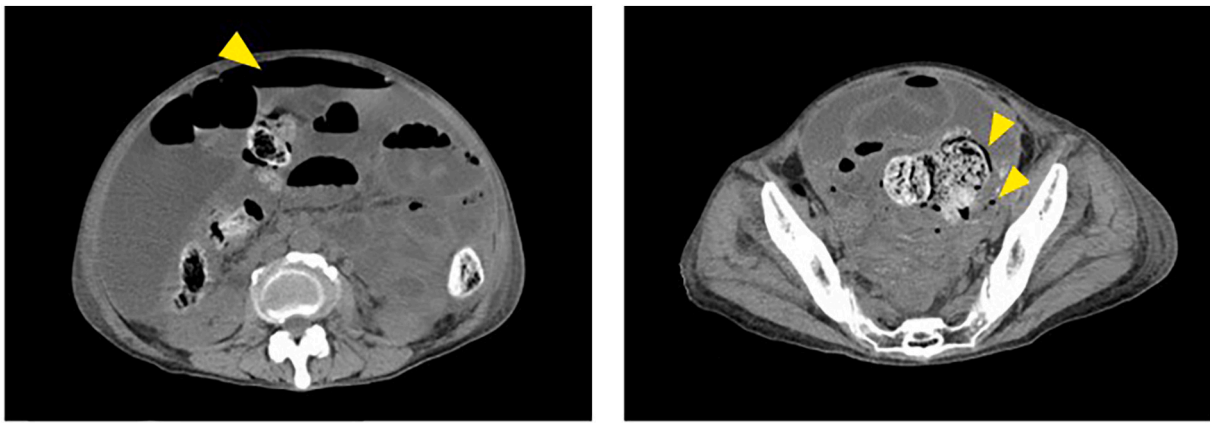


Fig. 3. CT on day12.

Simple CT shows a free space in the abdominal cavity that is not continuous with intestinal gas and is suspicious for intestinal perforation. It is difficult to identify the location of the perforation on imaging findings alone.

Howard et al. classified risk factors for TLS into those related to tumors and those related to patient's general condition [4]. The former includes large tumor size, multiple organ metastases, hepatomegaly, splenomegaly, nephromegaly, and urinary tract stenosis due to tumor invasion. The latter includes electrolyte abnormalities, hyperuricemia, dehydration, hypertension, diabetes, and decreased renal function. Electrolyte abnormalities, dehydration, and decreased renal function can be improved by fluid therapy, and the prophylactic drug rasburicase can effectively prevent hyperuricemia [5].

Since 1993, seven cases of TLS in ovarian cancer have been reported (Table 1) [6–12]. TLS has occurred regardless of histological type or chemotherapeutic drugs, with every case having a high-volume tumor. Spontaneous occurrence was reported in two cases, but symptoms appeared within a week after treatment in all cases except Case 2. Therefore, careful follow-up is necessary for at least a week after chemotherapy. TLS can be fatal, but still has a chance of recovery if treated appropriately. However, Gemici mentioned that mortality rate related to TLS is higher in solid tumors than in hematologic tumors due to malignancy and treatment-related complications [13]. In Case 4, TLS directly caused death. However, the three other cases (Cases 1, 2, and 6) also died due to complications that occurred shortly after TLS resolution. The mortality rate of 4 out of 7 cases (57%) is very high compared to the overall TLS mortality rate of 21% including hematological tumors, as reported in existing reports [1]. However, Caravaca-Fontan et al. reported a similarly high mortality rate of 63% in their case series of TLS in solid tumors [14]. This suggests that a large proportion of deaths from TLS in solid tumors, including ovarian cancer, are not due to TLS itself but due to complications secondary to TLS.

Generally, the most reported causes of death related to TLS are acute renal failure and cardiopulmonary dysfunction. In our case, renal function improved immediately after treatment, and CT performed 24 h before death showed neither cardiomegaly nor pleural effusion exacerbation. Therefore, intestinal perforation may have caused the recurrence of symptoms including vomiting and arrhythmia. Severe tumor adhesion, which could be an invasion, to the sigmoid colon was the main reason for perforation, and TLS probably enhanced it. It should be

acknowledged that serious complications may follow even after recovering from TLS.

Multiple peritoneal implants or intestinal adhesions are common in advanced ovarian cancer. Therefore, to prevent or predict intestinal perforation, intestinal wall invasion should be evaluated before chemotherapy using a stool hemoglobin test or a colonoscopy, as necessary.

TLS also occurs spontaneously, however, most cases are triggered by chemotherapy. Patients and families should be informed of TLS risk before chemotherapy since it can be potentially life-threatening. In cases of TLS, it is important to explain the ever-changing situation to the family without delay while quickly proceeding with treatment. If saving a patient's life seems difficult, active treatment and palliative treatment must be proposed to ensure that the patient is pain-free and comfortable during their last days of life.

4. Conclusion

TLS occurs in both hematologic malignancies and solid tumors. The risk of TLS is particularly high in ovarian cancer due to high chemosensitivity and tumor volume. In addition, advanced ovarian cancers may invade the intestinal tract. Therefore, even when TLS is treatable, intestinal perforation should be considered. TLS in ovarian cancer is relatively predictable, and prophylactic measures are of foremost importance.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

All authors have no conflicts of interest to disclose.

Table 1
Reviews of case reports on tumor lysis syndrome (TLS) in ovarian cancer.

| Age (years) | Histological type | Primary/recurrent | Residual tumor at the onset of TLS | Preceding treatment | Line(s) of chemotherapy | TLS onset after treatment | Outcome of TLS | Complication immediate TLS | Author | Year | Reference number |
|-------------|-------------------|-------------------|---|-------------------------------|-------------------------|----------------------------|----------------|---|-------------|------|------------------|
| 1 | HGSC | Primary | Partial ovarian tumor, massive peritoneal dissemination | Carboplatin | 1 | 96 h | Improved | Rapid tumor growth | Bilgrami SF | 1993 | [5] |
| 2 | HGSC | Recurrent | Bulky lymph node swelling, massive peritoneal dissemination, | Cyclophosphamide Topotecan | 3 | 14 days after second cycle | Improved | Ileus | Chan JK | 2005 | [6] |
| 3 | CCC | Recurrent | Ascites, bulky multiple peritoneal dissemination, | Paclitaxel | 3 | 5 days | Improved | | Yahata T | 2006 | [7] |
| 4 | HGSC | Recurrent | Bulky lymph node swelling, 2.5-cm-sized mediastinal mass, multiple lung metastasis, extensive intravascular tumor | Carboplatin Paclitaxel | 4 | 2 days | Death | Respiratory failure, coagulopathy, ischemic hepatitis | Camarata M | 2012 | [8] |
| 5 | EC | Primary | >20-cm-sized ovarian tumor, 3300 mL ascites | None | NA | NA | Improved | | Okamoto K | 2015 | [9] |
| 6 | Yolk sac tumor | Primary | 9 × 8-cm-sized endometrial mass, 13 × 10-cm-sized adnexal mass | Radiation | NA | 3 days | Improved | Sepsis | VanHise K | 2017 | [10] |
| 7 | HGSC | Primary | Omental cake, ascites, pleural fluid | None | NA | NA | Improved | | Shukla DK | 2017 | [11] |

HGSC = high-grade serous carcinoma; CCC = clear cell carcinoma; EC = endometrioid carcinoma.

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Ethical approval

This case report was approved by our hospital's Ethics Committee.

Consent

Written informed consent was obtained from the patient's family for publication of this case report and accompanying images because the patient died. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Saki Kunimoto: writing the draft of this manuscript and clinical management; Lena Tashima: clinical management, supervision, and review and editing of this manuscript; Kimihiko Ito: supervision and review and editing of the manuscript; and Kensuke Hori: review and editing of the manuscript.

Registration of research studies

This paper is a case report and was therefore not required to be registered with any registry.

Guarantor

Kimihiko Ito.

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