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Case report

Spontaneous tumor lysis syndrome occurring in untreated uterine cancer

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1. Introduction

Tumor lysis syndrome (TLS) is an oncologic emergency caused by massive lysis of tumor cells and release of intracellular contents. It is characterized by laboratory findings of hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Clinical complications include renal failure, cardiac arrhythmias, and seizures (Cairo and Bishop, 2004). TLS is seen most commonly in hematologic malignancies and typically occurs after the initiation of cytotoxic treatment. Spontaneous TLS occurs in the absence of therapeutic intervention due to spontaneous death of rapidly dividing tumor cells. This condition is rare in solid tumors and even more so in gynecologic cancers (Jasek and James Day, 1994; Kekre et al., 2012; Weeks and Kimple, 2015). There is only one report in the literature of spontaneous TLS in ovarian cancer and one in an undifferentiated ovarian/endometrial carcinoma (Okamoto et al., 2015; Thapa et al., 2013). The only report of TLS in a patient with endometrial carcinoma occurred after initiation of chemotherapy in a recurrent setting (Godoy et al., 2010). We report two cases of spontaneous tumor lysis syndrome, one in a chemotherapy naïve patient with primary endometrial adenocarcinoma and one in a patient with a history of diffuse large B cell lymphoma diagnosed with a second primary uterine serous carcinoma.

2. Case 1

A 33-year-old G2P1011 premenopausal woman with past medical history significant for irregular menses presented to the emergency department (ED) with 5 days of worsening diffuse abdominal pain and 2 months of abnormal vaginal bleeding. She reported a 10 lb. weight-gain over the previous few weeks associated with nausea, early satiety, and abdominal distension. Family history was negative for any malignancies. Physical exam showed 18-week size uterus, firm pelvic immobile mass, and right abdominal tenderness. Transvaginal ultrasound showed a mass in the uterine fundus, 3.7 cm irregular left ovary, 14.2 cm right ovarian mass, and a small amount of pelvic free fluid. Hemoglobin was 6.7 and 2 units of packed red blood cells were transfused. Endometrial biopsy demonstrated grade 1 endometrioid endometrial adenocarcinoma, ER/PR +, p16 negative.

The plan was to proceed with exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy (TAH/BSO), however in the interim she presented to another facility with severe abdominal pain and worsening distension. Abdominal computed tomography (CT) demonstrated massive ascites, bilateral ovarian masses, peritoneal implants, and endometrial thickening. A CA125 on admission was > 600 U/mL. She was admitted for paracentesis and discharged a week later. Cytology was consistent with metastatic adenocarcinoma.

The patient then presented to our institution 2 days later for persistent abdominal pain. A CA 125 on admission was 1512 U/mL. Laboratory results over the course of her medical care are detailed in Table 1. Labs on admission showed leukocytosis, hyperkalemia, and elevated LDH. The next day, labs met criteria for tumor lysis syndrome, demonstrating a severe metabolic acidosis. The patient subsequently underwent exploratory laparotomy, TAH/BSO, omentectomy, appendectomy, diaphragm stripping, and debulking. Pathology was consistent with grade 1 stage IVB endometrioid endometrial carcinoma with extensive metastases involving the endometrium, bilateral ovaries, bladder, peritoneum, omentum, liver, and right hemidiaphragm. Laboratory abnormalities resolved postoperatively. Patient was discharged on postoperative day 7. She completed 6 cycles of paclitaxel and carboplatin. Six months later, a biopsy of a bleeding vaginal mass revealed recurrence. Subsequent PET CT showed a mass in the pelvis and pancreatic head with extensive peritoneal, diaphragmatic, and mesenteric nodal disease. She is currently receiving second line chemotherapy.

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Table 1
Pertinent lab values from the course of treatment in Case 1.

	Primary ER visit		Regional center admission			Surgical admission								
Operative date														
Lab values Dates (2016)	5/18	5/19	6/25	6/28	7/1	7/3	7/4	7/5	7/6	7/7	7/8	7/9	7/10	7/13
WBC (K/cmm)	21	21	21.8	26.3	27.2	30.8	39.6	39.5	38.6	34.7	25.4	24.2	19.5	16.3
Hgb (g/dL)	6.7	9	7.9	11.5	11.4	11	11.4	10.5	10.7	10.4	8	7.8	10.2	9.8
Hct (%)	23.8	29.9	27.7	37.8	36.8	37.7	38.8	34.7	34.9	31.3	25.1	25.9	31.6	32
Platelets (K/cmm)	654	542	910	916	734	865	915	798	810	396	342	381	370	418
BUN (mg/dL)	7	–	–	16	29	34	45	44	48	39	25	10	10	4
Creatinine (mg/dL)	0.7	–	0.9	1	**2.2**	**1.8**	**2.66**	**2.86**	**3.17**	**2.05**	0.88	0.59	0.44	0.41
ALT (U/L)	33	–	15	–	–	9	14	19	19	202	–	126	102	75
AST (U/L)	40	–	35	–	–	69	35	37	31	688	–	268	151	121
Total Bilirubin (mg/dL)	0.6	–	0.5	–	–	1.3	0.9	0.9	0.8	3.8	–	4.5	3.6	1.3
LDH (U/L)	–	–	–	–	–	1111	–	–	803	–	650	685	–	–
Sodium (mmol/L)	137	–	140	135	129	122	125	124	124	132	137	138	137	136
Potassium (mmol/L)	4.6	–	4.1	5	5.1	**6.8**	**6.1**	**4.8**	**4.9**	**4.9**	4.2	4.4	4	4
Chloride (mmol/L)	100	–	106	103	98	93	90	91	93	102	106	107	107	104
Calcium (mmol/L)	8.8	–	–	9.9	**9.3**	**8.7**	**9.4**	**8.6**	**8**	**7.7**	7.5	7.6	7.5	7.3
Albumin (g/dL)	3.7	–	2.5	–	–	2.9	2.8	2.6	2.4	2.1	–	2	2.1	2
Uric Acid (mg/dL)	–	–	–	–	–	–	**12.8**		**13**	–	**5.2**	3.2	–	–
Phosphate (mg/dL)	–	–	–	–	–	–	**7.2**	**7.6**	**9.4**	**6.4**	3.5	2.8	2.2	2.2

Bold values are lab abnormalities pertinent to diagnosis of spontaneous TLS in case 1.

3. Case 2

A 65 year old G4P2022 postmenopausal woman with a history of diffuse large B cell lymphoma (DLBCL) stage 1AE (A denotes lack of B symptoms and E indicates isolated site of extra-nodal spread) involving the colon, hypertension, type 2 diabetes, hypothyroidism, and systolic heart failure with an automated implantable cardioverter defibrillator (AICD) secondary to doxorubicin was referred to gynecologic oncology for evaluation of increased metabolic activity (SUV 5.1) in the uterus on post treatment PET/CT. DLBCL was treated with transverse colectomy and 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) achieving remission by CT. Transvaginal ultrasound showed endometrial thickening. She subsequently presented to the ED with 2 days of vaginal bleeding and abdominal cramping. Laboratory studies were normal and repeat transvaginal ultrasound was notable for interval increase in endometrial thickness and focal heterogeneous endometrial structure.

She was followed as an outpatient by hematology/oncology and repeat PET/CT 5 months after the initial study was notable for interval development of hypermetabolic aortocaval, bilateral common and internal iliac lymphadenopathy, maximum SUV 12.0, and persistent diffuse hypermetabolic activity of the uterus and cervix. Gynecologic history included menopause at 47 and no history of abnormal pap smears. Family history was negative for any malignancies. On physical exam the cervix had a nodular appearance with diffuse parametrial induration, minimally mobile uterus, but no adnexal masses appreciated. She underwent hysteroscopy, dilation and curettage, endocervical curettage, and cervical biopsy. Pathology revealed serous carcinoma in all samples, most consistent with second uterine primary with cervical extension.

Two days later she was admitted to hematology oncology for previously planned salvage chemotherapy with rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) for suspected recurrence of DLBCL. Pre-chemotherapy labs met criteria for TLS. She was treated with rasburicase, allopurinol, sevelamer, and IV fluids. Chemotherapy was held. It was unclear whether lymphadenopathy on PET/CT was due to DLBCL recurrence or uterine carcinoma metastasis. CT guided biopsy of paracaval lymph node was consistent with uterine serous adenocarcinoma stage IVB. TLS resolved with treatment and on hospital day 7, chemotherapy was initiated with paclitaxel and carboplatin. She tolerated chemotherapy well and was discharged on hospital day 11. She received 3 cycles of chemotherapy, after which she suffered pancytopenia, pneumonia, heart failure exacerbation, intracranial hemorrhage secondary to thrombocytopenia, and acute on chronic renal failure, subsequently dying in the hospital.

4. Discussion

TLS occurs when tumor cells lyse, releasing nucleic acids. The purines are then broken down into uric acid, which in high concentrations leads to the acute kidney injury and subsequent metabolic abnormalities seen in the syndrome. In 2004, Cairo and Bishop proposed a definition and grading scale for TLS based on laboratory findings and clinical scenarios (Tables 2 and 3). Case 1 met criteria for TLS with a uric acid of 12.8 mg/dL, potassium of 6.1 mmol/L, phosphorus of 7.2 mg/dL, and creatinine 2.66 mg/dL. Based on the Cairo-Bishop grading scale, the patient in case 1 had grade 2 TLS. Her lab results normalized after surgical removal of tumor burden. Case 2 met criteria for TLS with calcium 6.3 mg/dL, phosphorus 5.4 mg/dL and uric acid 9.8 mg/dL prior to initiating chemotherapy, with Cairo-Bishop score of 1.

TLS is most commonly associated with hematologic malignancies after initiation of chemotherapy. The occurrence after chemotherapy in solid tumors and spontaneous occurrence in solid tumors is found mostly in case reports. We are aware of only 3 previous reports of TLS in ovarian or uterine cancers, of which 2 were spontaneous TLS. One case reported in 2010 was a patient who developed TLS after

Table 2
Cairo-Bishop criteria for tumor lysis syndrome in adults. Two or more criteria must be present within 3 days prior or 7 days after starting chemotherapeutic agents. Upper limit of normal (ULN).

	Factor	Value
Laboratory tumor lysis	Uric acid	≥ 8 mg/dL or 25% increase from baseline
	Potassium	≥ 6 mEq/L or 25% increase from baseline
	Phosphorus	≥ 4.5 mg/dL or 25% increase from baseline
	Calcium	≤ 7 mg/dL or 25% decrease from baseline
Clinical tumor lysis	Creatinine	≥ 1.5 × ULN
	Arrhythmia/sudden cardiac death	
	Seizures	

Table 3
Cairo-Bishop grading of tumor lysis syndrome in adults.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Laboratory Criteria	−	+	+	+	+	+
Creatinine	≤ 1.5 × ULN	1.5 × ULN	> 1.5–3 × ULN	> 3–6 × ULN	> 6 × ULN	Death
Arrhythmia	None	Intervention not required	Non-urgent medical intervention required	Symptomatic and not controlled with medication or controlled with device	Life threatening	Death
Seizure	None	None	One brief seizure or well controlled and not interfere with ADL	Altered consciousness, poor control, breakthrough medical therapy	Prolonged, repetitive, difficult to control	Death

Present (+), Upper limit of normal (ULN), Activities of daily living (ADL).

carboplatin/paclitaxel for recurrent endometrial carcinoma (Godoy et al., 2010). She presented 4 days after chemotherapy with shortness of breath, weakness, and fatigue. She was found to have TLS and a creatinine of 3.2. She died on hospital day 2 despite aggressive intervention including dialysis. This case differs from the ones presented above since it was not spontaneous but rather was related to chemotherapy, as is more typical of TLS. The second case reported in 2013 described spontaneous TLS, however the pathology was poorly differentiated carcinoma of gynecologic origin (Thapa et al., 2013). The pathology of the first case reported here was well-differentiated endometrial adenocarcinoma and of the second case was serous uterine carcinoma. Finally, a novel case of spontaneous TLS was reported in 2015, however it was in a patient with endometrioid ovarian carcinoma (Okamoto et al., 2015). The patient presented with a complaint of abdominal and back pain, and was found to have a > 20 cm pelvic mass and massive ascites. Laboratory studies fulfilled criteria for TLS. Surgical resection was performed to reduce the tumor burden. Postoperatively the patient improved and TLS resolved after intensive care. The patient received 6 cycles of carboplatin and docetaxel and at 8 months follow-up had no signs of recurrence.

Risk factors for developing TLS include tumor burden, proliferative ability and therefore sensitivity to chemotherapy, and dehydration or acute kidney injury leading to faster accumulation of cellular metabolites (Kekre et al., 2012; McBride and Westervelt, 2012). The patient discussed in case 1 had multiple risk factors for TLS including extensive metastasis with high tumor burden and renal insufficiency based on creatinine that more than doubled prior to admission. Likewise, the patient in case 2 had a large tumor burden with extensive regional lymphadenopathy.

Although TLS is rare, it is important to consider it in cases of solid tumors due to the high mortality rate associated with this syndrome. One large study found the hospital mortality rate of TLS to be 14.4% (Pathak et al., 2014). Another study found that with TLS related renal injury; hospital mortality rates were up to 51% (Darmon et al., 2010). Common measures to prevent TLS include IV hydration and urine alkalization to maintain urinary output and prevent uric acid deposition. Allopurinol can be used to prevent uricemia unless uric acid levels are already elevated, in which case rasburicase is preferred (Cairo and Bishop, 2004). In conclusion, a high level of suspicion must be maintained to identify TLS to initiate treatment as soon as possible.

Conflict of interest

There are no conflicts of interests for any of the contributors to this case report.

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