



CASE REPORT

Spontaneous tumor lysis syndrome in colon cancer: a case report and literature review

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Introduction

Tumor lysis syndrome (TLS) is a well-described oncologic emergency. The syndrome is deemed spontaneous when it occurs before initiation of any cytotoxic or definite treatment. Here, we report a rare case of a 49-year-old woman diagnosed with metastatic colon cancer with extensive liver involvement manifesting with fatal spontaneous tumor lysis syndrome (STLS). Literature review revealed only one other case of spontaneous tumor lysis in colon cancer and 27 other cases of spontaneous tumor lysis in solid tumors, dating back to 1977 [1, 2]. We also compiled clinical data on patients with solid cancers presenting with STLS to better understand tumor characteristics, location, tumor burden, and eventual outcomes.

Key Clinical Message

Although tumor lysis syndrome is well described, it is rarely seen or suspected in solid malignancies. Early recognition of this entity is paramount in reducing morbidity and mortality. Treating physicians should be aware of this possibility in solid tumor patients with either bulky disease or extensive liver involvement.

Keywords

Colon cancer tumor lysis syndrome, solid tumors and spontaneous tumor lysis syndromes, spontaneous tumor lysis syndrome.

Case Presentation

A 49-year-old African American woman, who was in a normal state of health until two months prior to this current admission, presented with worsening abdominal pain associated with nausea, vomiting, loss of appetite, early satiety, and subjective weight loss. The patient also complained of postprandial abdominal pain in the right upper quadrant (RUQ), which was nonradiating. There were no associated hematemesis, hemoptysis, melena, bright red blood per rectum, dysuria, or frequency. Her past medical history included hypertension, gastroesophageal reflux, hyperlipidemia, and anemia. Her surgical history included a cholecystectomy done in 2011. Her family history was pertinent for a maternal grandmother who was diagnosed with breast cancer at the age of 62. Her social history was

negative for tobacco use, ethanol use, or any illicit drug use.

Investigations and treatment

Pertinent physical examination findings demonstrated a morbidly obese (BMI > 45) patient with right upper quadrant tenderness on deep palpation without any signs of peritonitis, and bilateral pitting edema up to the knees. The cardiovascular, pulmonary, and neurological examinations were grossly normal. Computerized tomography (CT) scan of the abdomen and pelvis revealed hepatomegaly of 27.5 centimeters width by 14.5 centimeters anteroposterior diameter with multiple hypo-attenuating lesions (Fig. 1D and F) along with mural thickening of the cecum. Pertinent laboratory findings at the time of presentation included: white blood cells: $12.14 \times 10^3/\mu\text{L}$, hemoglobin: 8.0 g/dL, platelets: $512 \times 10^3/\mu\text{L}$, potassium: 3.5 mmol/L, serum creatinine (Cr): 0.87 mg/dL, albumin: 2.7 g/dL, total bilirubin: 0.9 mg/dL, alanine aminotransferase: 57 U/L, aspartate aminotransferase: 212 U/L, alkaline phosphatase: 324 U/L, and a lactic acid: 2.3 mmol/L. CT-guided liver biopsy demonstrated metastatic adenocarcinoma. Subsequent colonoscopy and biopsy of a near-obstructing necrotic caecal mass (Fig. 1A and B) confirmed a moderately differentiated invasive adenocarcinoma. F-18 Fluorodeoxyglucose positron emission tomography and computerized tomography (FDG PET/CT) scan revealed diffusely intense, FDG uptake in the liver (max standardized uptake value of 19.9) (Fig. 1C and E). The patient's health progressively started deteriorating with increasing edema of bilateral extremities associated with worsening dyspnea. Doppler ultrasound of bilateral extremities was negative for deep vein thrombosis, and the ventilation–perfusion scan was negative for pulmonary embolism. Transthoracic echocardiogram was also within normal limits. At this time, the patient was found to be in tumor lysis with lactate dehydrogenase levels: 10,853 U/L, uric acid: 20.3 mg/dL, and serum creatinine: 3.9 mg/dL (Table 1). Ultrasound of kidneys showed normal renal parenchyma and no evidence of obstructive uropathy. All the supportive measures including allopurinol, intravenous fluids, rasburicase, and dialysis were initiated. Despite aggressive resuscitative efforts, patient succumbed to death soon from multiorgan failure.

Discussion

We present here a fatal case of spontaneous TLS (TLS) as a complication of metastatic colon adenocarcinoma. TLS is an oncological emergency precipitated by massive release of intracellular contents into the circulation, manifesting in distinct laboratory abnormalities including, but

not limited to, hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Along with kidney injury, each of these metabolic derangements has its own catastrophic consequences [3].

TLS is generally initiated by effective cytotoxic chemotherapy in a context of rapidly proliferating tumor or in patients with massive tumor burden. While TLS is most commonly seen in hematologic cancers, it can also be seen in solid malignancies with a large tumor burden [3]. Cytotoxic chemotherapy, targeted antibody therapy, radiation, and even glucocorticoids are all well known to precipitate TLS [3]. Spontaneous TLS can be defined as the TLS occurring in the absence of any definitive treatment [4]. The initial step for diagnosis of TLS is based on the laboratory findings in an appropriate clinical context. Hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia are the primary indicators of TLS [5]. Clinical tumor lysis syndrome is considered when the traditional laboratory findings of TLS lead to nausea, vomiting, diarrhea, lethargy, cardiac arrhythmias, seizures, or sudden death [4, 5]. The Cairo-Bishop definitions provide laboratory values for diagnosis as well as a grading system for TLS [5].

Care of the patient with established TLS should include astute monitoring of potassium, calcium, uric acid, phosphorous, lactate dehydrogenase and serum creatinine levels, along with cardiac monitoring and urine output. Hydration is a vital aspect of the treatment, and the remainder of the treatment is focused on specific electrolyte abnormalities, specifically management of hyperkalemia. [3]. Hyperkalemia is one of the earliest and most ominous signs, a harbinger of life-threatening arrhythmias, which warrants close telemetry monitoring [5]. A parallel approach of correcting hypocalcemia and hyperphosphatemia, which often coexist, is important to avoid calcium phosphate precipitation [3, 5]. Oral phosphorous binders not only decrease phosphorous levels, but also aid in correction of hypocalcemia [5]. Uric acid crystal deposition in the distal renal tubules can cause obstructive nephropathy, and this along with hyperphosphatemia can lead to acute renal failure [5–7]. Allopurinol can be used prophylactically in patients at risk of TLS to lower uric acid production. However, in patients with active TLS, allopurinol use may result in elevated levels of xanthine by inhibiting xanthine oxidase [6–8]. Xanthine may also precipitate in the renal tubules which can contribute to obstructive uropathy in a similar manner as uric acid. [7, 8]. For these reasons, rasburicase, which converts uric acid to soluble allantoin, is the recommended drug for hyperuricemia in tumor lysis syndrome [3, 4, 6, 7]. In patients with low urine output, persistent hyperphosphatemia, or hypocalcemia, dialysis needs to be initiated [3].

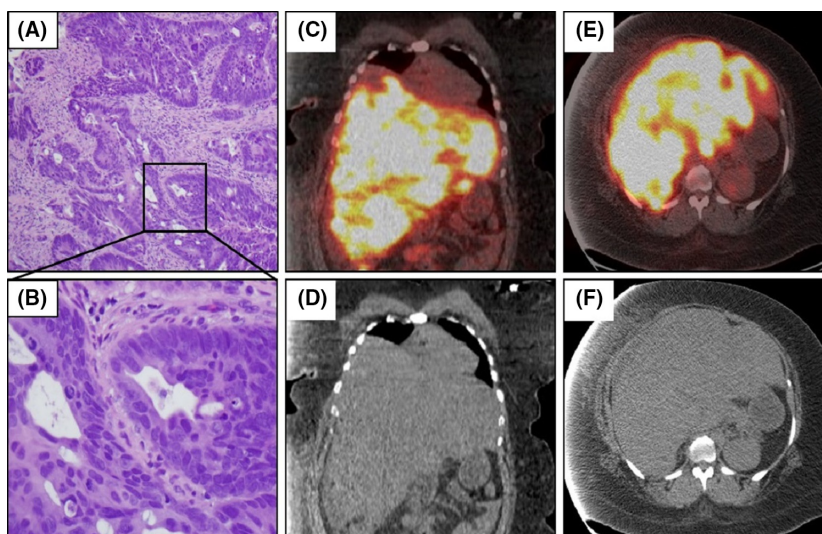


Figure 1. Biopsy of colonic mass and fused PET/CT images. H&E staining of colon mass at lower (A) and 40× (B) magnification. Fused PET-CT sagittal (B,C) and coronal sections (D,E) revealing very avid uptake in the liver.

Table 1. Laboratory trends in the patient presented.

Parameter	Day 1	Day 13	Day 21	Day 23
WBC (K/ μ L)	12.14	13.29	16.95	22.05
Hemoglobin (g/dL)	8	7.7	7.1	7.5
Platelets (K/ μ L)	512	563	390	222
Potassium (mmol/L)	3.5	4.5	5.0	5.4
BUN (mg/dL)	6	24	73	72
Creatinine (mg/dL)	0.87	1.9	3.9	4.8
Phosphorus	-	-	4.4	6.7
Calcium (mg/dL)	8.5	8.9	8.2	8.1
ALT (U/L)	57	122	121	175
AST (U/L)	212	635	603	954
Total Bilirubin (mg/dL)	0.9	2.2	4.9	6.0
Uric Acid (mg/dL)	-	-	20.3	6.3
LDH (U/L)	-	-	10853	>4000

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

The first reported case of spontaneous tumor lysis in a nonhematologic malignancy was reported in 1977 [2]. There have been 75–100 reported cases of tumor lysis in solid tumors, mostly after treatment, between 1977 and 2011 as described in the literature [6, 9]. STLS is considered rare in all types of malignancy, but according to a study by Tsokos et al., three of 33 patients with non-Hodgkin lymphoma already had hyperuricemia and kidney injury prior to treatment [10]. Therefore, spontaneous TLS may be underdiagnosed at least in hematologic malignancies. Our literature review revealed only one other case of spontaneous tumor lysis in a patient with colon adenocarcinoma [1]. This involved a

27-year-old man with a similar initial presentation as our patient.

Our literature review yielded 28 other cases of spontaneous tumor lysis in solid tumors (Table 2). There was a male predominance with 18 of 29 patients being male. The mean age at the time of diagnosis of STLS was 57.4 years. Although there was a variation in origin of primary tumors, extensive liver involvement is noted in 82.8% of total cases reported. When the liver is not involved, patients inevitably had a large tumor burden and necrosis. As noted by Gemici et al. [5], liver involvement seems to predispose patients to TLS. This may be due to a high purine pool in the liver which can be released during necrosis or impaired uric acid metabolism if hepatic function is impaired by a high tumor burden [5]. The most common presenting symptom was abdominal pain or discomfort, seen in 48.3% of the patients. With our patient included, the mortality rate of these cases approaches 69%. TLS in solid tumors is unpredictable and carries a worse prognosis when compared to hematologic malignancies [5]. There is a 20%–50% mortality in all cases of TLS in solid tumors if undiagnosed or if diagnosed too late [6, 11]. United States Food and Drug Administration has approved rasburicase in 2009 for the initial management of plasma uric acid levels in adult patients with hematological and solid malignancies who are receiving anticancer therapy, expected to result in TLS. This approval was based on a phase III, randomized, multicenter, open-label trial (EFC 4978) which demonstrated a significant improvement in uric acid response rates among patients treated with rasburicase compared to

Table 2. Published cases from 1977 until 2016 of spontaneous tumor lysis syndromes in solid tumors.

Case author	Age/ sex	Initial TLS symptom	Cancer type	Sites involved	Treatment	Initial outcome
Gbaguidi et al. [13]	88/F	Vomiting	Renal Ca.	Large renal + bone + liver	Unknown	Died
Okamoto et al. [14]	62/F	Abd distention	Uterine adeno Ca.	>20 cm pelvic mass + ascites	Chemo, surgery	Survived
Saleh et al. [15]	56/F	Fatigue	Pancreatic adeno Ca.	Large pancreatic mass + liver	All, Rasb, K Binders	Died
Wang et al. [16]	71/F	Skin nodules	GI or ovarian adeno Ca.	Skin + renal + adrenal + lung + liver	All, K Binders, Alk	Died
Frestad et al. [1]	27/M	Abd Pain	Colon mucinous adeno Ca.	Liver + lung + pleura + LAD	Rasb, fibrinogen	Died
Norberg et al. [17]	56/M	Back Pain	Renal Ca.	10 cm Renal mass + liver + bone + lung	Fluids, all, HD	Died
Zakharia et al. [18]	49/F	Abd Pain	Spindle cell sarcoma	9 cm RP mass + liver + lung	Fluids, Rasb, HD	Died
Goyal et al. [19]	51/M	Weakness	Gastric adeno Ca.	Liver + bone + adrenal + LAD	Fluids, All, HD	Survived
Ali et al. [20]	66/M	Abd Pain	Cholangiocarcinoma	Extensive liver involvement	Fluids, All	Died
Mehrzad et al. [21]	70/M	Unresponsive	Hepatocellular Ca.	14 cm liver mass + LAD	Fluids, Alk	Died
Mouallem et al. [22]	69/M	Rectal Bleed	Melanoma	Extensive liver involvement	Fluids	Died
Saini et al. [23]	59/F	Vomiting	CUP: adeno Ca.	Large RP mass + liver + LAD	Fluids, Rasb, HD	Died
Kekre et al. [24]	76/M	Vomiting	Hepatocellular Ca.	19 cm liver mass	Fluids, All, HD	Died
Goyal et al. [25]	51/F	Anuria	Ductal breast Ca.	4 cm ulcerated breast mass	Fluids, All	Died
Murray et al. [26]	13/F	Abd distention	GCT	20 cm pelvic mass + peritoneum	Rasb, Chemo	Survived
D'Alessandro et al. [27]	22/M	Abd distention	GCT: choriocarcinoma	14 cm RP mass + lung + liver	Rasb, K Binders	Died
Abboud et al. [28]	53/M	Abd Pain	Sq. cell Ca./maxillary sinus	Extensive liver involvement	All, Alk, Rasb	Died
Shenoy. [29]	74/M	Anuria	Squamous cell Ca- lung	Bulky necrotic lung mass	All, HD, Chemo	Survived
Lin et al. [30]	72/M	Anorexia	Prostate Ca.	Extensive liver + bone involvement	All, Furosemide, HD	Died
Vaisban et al. [31]	82/F	Weakness	Colon Ca.	Extensive liver involvement	All, Alk	Survived
Vaisban et al. [31]	80/M	Abd Pain	Pheochromocytoma	20 cm Adrenal mass	All, Alk	Survived
Vaisban et al. [31]	72/M	Weakness	Hepatocellular Ca.	Large liver lesion	All, Alk	Died
Pentheroudakis et al. [32]	52/M	Abd pain	GCT: endodermal sinus	RP LAD + liver + lung	HD, Chemo	Survived
Pentheroudakis et al. [32]	24/M	Abd pain	GCT: Seminoma	25 cm RP mass + liver	HD, Chemo	Survived
Woo et al. [33]	36/M	Abd distention	Gastric adeno Ca.	7 cm gastric mass + liver + LADs	Alk, All, HD, Chemo	Died
Feld et al. [34]	72/M	Abd distention	Lung adeno Ca.	Large lung mass + liver	Cal, K Binders, All	Died
Sklarin et al. [35]	62/F	Bone pain	Inflammatory breast Ca.	Breast + liver + lung + bone marrow	All, Chemo	Survived
Crittenden et al. [2]	50/M	Abd distention	CUP: adeno Ca.	Extensive liver + bone + LAD	All, Alk	Died

Abd, abdominal; All, allopurinol; Alk, alkalinization; Ca, carcinoma; Cal, calcium supplementation; Chemo, chemotherapy; CUP, carcinoma of unknown primary; F, female; HD, hemodialysis; GCT, germ cell tumor; K Binders, potassium Binders; M, male; Mets, metastases; Rasb, rasburicase; RP, retroperitoneal; Sq Cell Ca, squamous cell carcinoma.

those receiving allopurinol [12]. The mortality rate for our reviewed cases of spontaneous tumor lysis syndrome in which rasburicase was used is 87.5%. Whether rasburicase use, which is currently increasing, can contribute to increased survival is unknown secondary to very few cases of STLS in solid tumors reported in the literature.

Conclusion

We believe that spontaneous TLS is an underdiagnosed and overlooked entity which is associated with poor outcomes. High index of suspicion for STLS should be exercised while managing patients with bulky disease, extensive liver involvement, or concurrent renal

dysfunction. As laboratory testing for uric acid and LDH is universally available and can be easily performed, early recognition and aggressive management should be pursued to potentially reduce organ dysfunction and fatal outcomes.

Authorship

DS, PP, and AT: were responsible for manuscript preparation. RS: involved in pathology contribution and manuscript editing. All the authors: have approved the final manuscript.

Conflict of Interest

None declared.

Patient consent

Obtained.

Provenance and peer review

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