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CASE REPORT

Colorectal Cancer-Associated Spontaneous Tumor Lysis Syndrome: a Case Report and Review of the Current Literature

Matthew R. Kearney[1] · Emerson Y. Chen[1] · Peter Stenzel[2] · Christopher L. Corless[2] · Thomas G. Deloughery[1] · Mark Zivney[2] · Charles D. Lopez[1]

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Background

Tumor lysis syndrome (TLS) represents an oncologic emergency caused by the destruction of malignant cells and subsequent release of intracellular contents into the bloodstream. TLS is characterized by a constellation of laboratory abnormalities: hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. TLS can be defined by the Cairo Bishop criteria [1], which defines laboratory TLS (TLS with only laboratory abnormalities and absent clinical manifestations) and clinical TLS. Tumor-specific risk factors for TLS include the proliferation rate, sensitivity to treatment, and baseline tumor burden while patient-specific risk factors include pre-existing kidney disease, and volume status [2]. Cellular lysis can occur in the setting of either systemic treatment or localized radiation; alternatively, spontaneous TLS can occur in the absence of any therapeutic intervention. As cellular breakdown products are released into the bloodstream, uric acid and calcium phosphate crystals can precipitate in the renal tubules. Acute renal failure may occur due to deposition of crystals in the tubules and by crystal-independent mechanisms of hyperuricemia-induced renal injury [3]. The resulting electrolyte disturbances may precipitate cardiac arrhythmias and seizures.

Quick identification of TLS is critical as treatment involves early aggressive hydration to increase renal perfusion and urine output and therefore decrease the risk of crystal precipitation, and correction of electrolyte abnormalities. The administration of allopurinol and rasburicase to target the purine metabolism pathway is also important to decrease serum uric acid levels.

TLS most commonly occurs in the setting of treatment of hematologic malignancies. It is a much rarer sequela of solid tumors, though it has been reported in small cell lung cancer, hepatocellular carcinoma, and breast cancer, among other solid malignancies [4]. It most often occurs in the setting of treatment with cytotoxic chemotherapy. Spontaneous tumor lysis in solid tumors is an even rarer phenomenon. Here, we present a case of severe spontaneous tumor lysis in a patient with metastatic colorectal cancer (CRC), who developed multi-organ failure and died within days.

Case

A 47-year-old woman with a past medical history of hypertension initially presented to her primary care doctor 10 days before her hospitalization with 1 week of epigastric abdominal pain with radiation to the right flank. Her vitals were unremarkable at that time. Her laboratory evaluation was notable for INR of 1.36, AST of 84, ALT of 60, and ALK of 142. A right upper quadrant ultrasound demonstrated innumerable nonspecific hypoechoic liver lesions.

Four days later, she presented to the emergency department with worsening abdominal pain. Her creatinine at that time was 1.04 (baseline 0.5–0.8), with elevation of AST to 203, ALT to 110, and alkaline phosphatase to 273. As shown in Fig. 1, a CT with contrast of the abdomen and pelvis demonstrated mass-like asymmetric mural thickening of the sigmoid colon, innumerable lesions throughout the liver, the largest of which measured 7.3 × 7.2 cm in the left lobe, and prominent lymphadenopathy throughout the abdomen and pelvis, the largest of which was a porta hepatis node measuring 3.3 × 1.8 cm. She was referred to gastroenterology for expedited

✉ Charles D. Lopez
lopezc@ohsu.edu

[1] Knight Cancer Institute, Oregon Health and Sciences University, 3181 SW Sam Jackson Park Rd L-586, Portland, OR 97239, USA

[2] Department of Pathology, Oregon Health and Sciences University, Portland, OR, USA

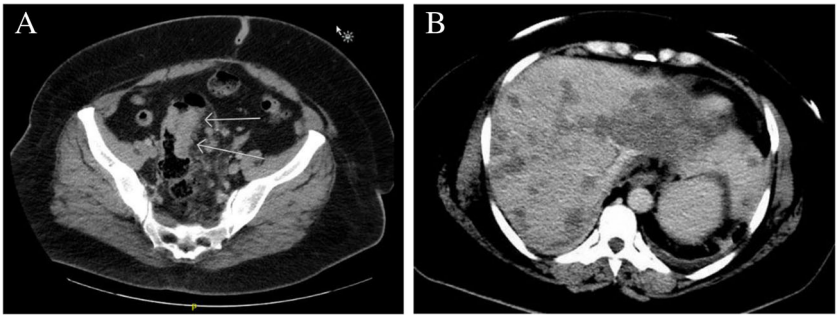

Fig. 1 CT abdomen and pelvis demonstrating **a** asymmetric mural thickening of the sigmoid colon and **b** innumerable liver lesions consistent with metastatic disease

colonoscopy and tissue diagnosis. However, over the ensuing 6 days, she declined clinically and required hospitalization for continued abdominal pain, nausea, and inability to tolerate oral intake. On admission, her laboratory values were remarkable for leukocytosis of 16.3, INR of 2.15, Na of 126, K of 5.9, BUN of 100, and creatinine of 6.5. Her liver function tests showed AST of 923, ALT of 345, alkaline phosphatase of 885, and total bilirubin of 6.4. Other values included lactate 7.1, uric acid 23.1, phosphorus 8.1, calcium 7.4, and LDH 3071. A repeat CT abdomen and pelvis without contrast demonstrated no biliary ductal dilatation but increased hepatomegaly and hepatic edema suggestive of worsening hepatitis. A trend of relevant laboratory values can be seen in Fig. 2.

She was started on IV fluids, allopurinol, and rasburicase, and treated for hyperkalemia. However, over the course of the next few hours, she became increasingly oliguric with refractory hyperkalemia to 6.6 and was transferred to the intensive care unit (ICU) for urgent dialysis. Her infectious workup remained negative despite persistent lactic acidosis. A liver biopsy was obtained on the day following her admission, and a CT chest without contrast revealed no thoracic metastases. Her CEA was mildly elevated at 2.9 ng/mL. Preliminary review of the liver biopsy was consistent with a carcinoma and ruled out small cell carcinoma histology or a lymphoma.

On day 2 of ICU admission, she had increasing encephalopathy from acute liver failure despite her uremia improving with dialysis. A CT of the head was unremarkable, and extensive serology workup for concomitant liver disease was negative. A repeat liver ultrasound with Doppler showed patent hepatic and portal veins with normal antegrade flow and no evidence of any thrombus. On ICU day 3, she developed worsening hypotension attributed to distributive shock secondary to TLS and liver failure, though broad spectrum antibiotics were continued and infectious workup remained negative. On ICU day 4, she was intubated due to worsening mental status, multi-organ dysfunction, and persistent shock. Final pathology from her liver biopsy demonstrated poorly differentiated adenocarcinoma consistent with a colorectal primary. After discussions with family members, she was ultimately transitioned to comfort care, and she died a few hours later.

At autopsy, the liver weighed 5860 g (normal weight range is 1500 to 1800 g) with a smooth surface. On section, the parenchyma was mottled red and orange with areas of apparent hemorrhage and necrosis (Fig. 3a). In the sigmoid colon, there was a lobated 7 × 5 × 1.5 cm tumor that extended from lumen to mesentery. By microscopy, the sigmoid colon tumor was identified as poorly differentiated adenocarcinoma (Fig. 3b). A similar appearing tumor was found throughout the liver with extensive necrosis and widespread tumor thrombi in portal vein branches (Fig. 3c). Microscopic tumor deposits were present in both lungs. Many lymph nodes were found throughout the cervical, thoracic, and abdominal area; microscopic exam of a selected mediastinal lymph node demonstrated near total replacement with tumor and necrosis. The patient's tumor underwent next-generation sequencing using a 124 gene panel (GeneTrails Solid Tumor Panel), which

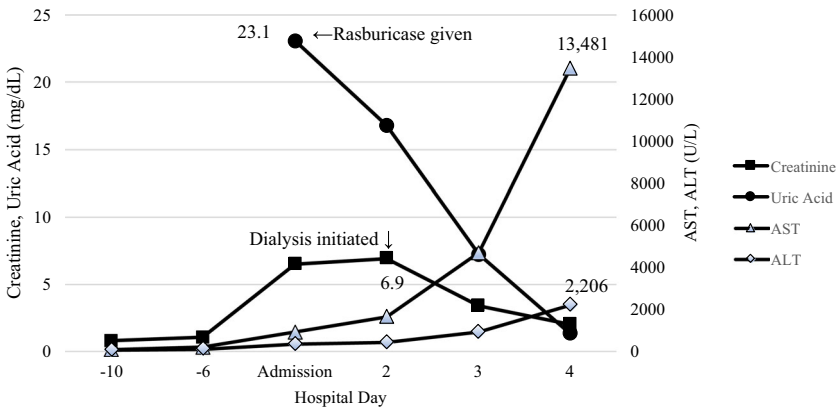

Fig. 2 Selected laboratory trends over time

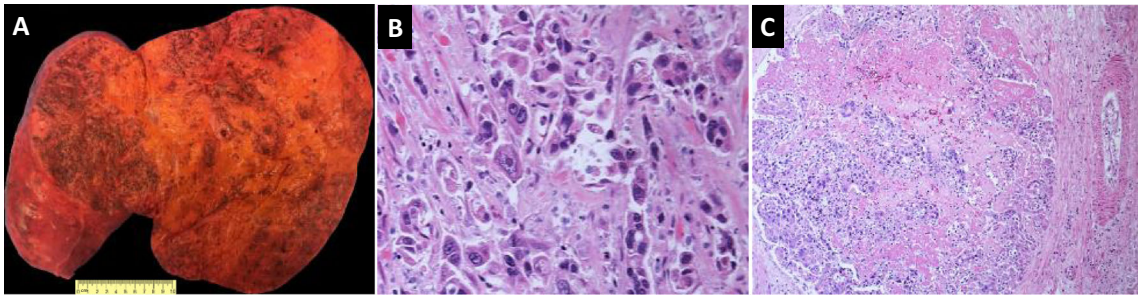

Fig. 3 Autopsy findings. **a** Enlarged liver with hemorrhage and necrosis. **b** Poorly differentiated colonic adenocarcinoma. **c** Portal vein branch with tumor thrombus

demonstrated the following alterations: HRAS p.Q61K, APC p.T1556fs*3 and p.R332* and p.Y493fs*5, CDNK2A p.A137, TP53 p.C135fs*35 and gene copy number loss, and NTRK1 p.P689L. This panel also revealed the tumor had no BRAF or mismatch repair mutations. The full panel of genes analyzed is listed in Table 1.

Discussion

Here, we present a case of spontaneous TLS in a patient with metastatic CRC. Spontaneous TLS in a non-lymphomatous solid tumor was first reported in 1972 by Crittenden and Ackerman who described a case of hyperuricemic acute renal failure in a patient with disseminated anaplastic gastrointestinal adenocarcinoma and bulky liver metastases [5]. A review of TLS in solid malignancies in 2012 found that of 100 documented cases of solid tumor TLS from 1977 to 2001, only 14% were spontaneous, while the remainder were associated with some form of treatment, 58% of which were chemotherapy induced [4]. In that review, the three most common solid tumors associated with TLS were small cell lung cancer, hepatocellular carcinoma, and breast cancer. Additionally, the most important risk factors for solid tumor associated TLS were large tumor burden and liver metastasis; 83% of patients had metastatic disease, most commonly in the liver [4]. These findings were consistent with an earlier report [6] which noted liver metastasis was present in most solid tumor-associated TLS. Whether liver metastasis is simply a reflection of increased tumor burden or is an independent risk factor for TLS due to decreased capacity for purine and uric acid metabolism is unclear [4]. There is currently no definition for

Table 1 124-gene next-generation sequencing panel at OHSU (GeneTrails Solid Tumor Panel)

AKT1	CDKN1B	FANCM	KIT	NTRK1	RAD51D
AKT2	CDKN2A	FGF18	KRAS	NTRK2	RAD52
AKT3	CHEK1	FGF19	MAP2K1	NTRK3	RAD54L
ALK	CHEK2	FGF3	MAP2K2	PALB2	RAF1
APC	CTNNB1	FGF4	MAP2K4	PDCD1LG2	RASA1
AR	DDR2	FGFR1	MAPK1	PDGFRA	RB1
ARAF	DDX11	FGFR2	MDC1	PIK3CA	RET
ARID1A	EGFR	FGFR3	MDM2	PIK3CB	RICTOR
ATM	ERBB2	FGFR4	MDM4	PIK3R1	RIT1
ATR	ERBB3	GNA11	MET	PMS1	ROS1
BAP1	ERBB4	GNAQ	MLH1	PMS2	RPTOR
BARD1	ERCC2	GNAS	MLH3	POLE	STAG2
BRAF	ERCC5	HIST1H3B	MRE11A	PPP2R1A	STAT3
BRCA1	ESR1	HRAS	MSH2	PPP6C	STK11
BRCA2	FAM175A	IDH1	MSH6	PTCH1	TOP1
BRIP1	FANCA	IDH2	MTOR	PTEN	TP53
CASP8	FANCC	IDO1	MUTYH	RAC1	TSC1
CCND1	FANCD2	IDO2	MYC	RAD50	TSC2
CCNE1	FANCE	INPP4B	NBN	RAD51	XRCC1
CD274	FANCF	JAK2	NF1	RAD51B	
CDK12	FANCG	KDR	NRAS	RAD51C	

what constitutes a large tumor burden, but high hepatic tumor burden should be noted in newly diagnosed solid tumors with regard to the risk of TLS. However, spontaneous tumor lysis syndrome is still possible without hepatic metastases [7]. Furthermore, recent reports of spontaneous TLS in metastatic malignancy of prostatic, ovarian, and endometrial origins shared the presence of poorly differentiated or high histologic grade, suggesting that this is likely another important risk factor for spontaneous TLS [8–10]. Therefore, obtaining baseline and post-treatment LDH and uric acid levels should be considered in patients with bulky metastatic disease with poorly differentiated histology.

With regard specifically to CRC, a 2014 review of solid tumor TLS cases from the years 1950 to 2014 reported seven cases of TLS associated with CRC [11]. Only one of these cases was spontaneous while all others were associated with chemotherapy [12]. On literature review via PubMed using the terms "tumor lysis syndrome" and "colorectal cancer," we found 13 cases of colorectal cancer-associated tumor lysis syndrome [12–24], which are summarized in Table 2. Four patients developed spontaneous CRC-associated TLS [12–15] and in the remaining nine patients, TLS was associated with chemotherapy. Thus, we present the fifth case of spontaneous CRC-associated TLS. The reported mortality associated with CRC-associated TLS is high, which is consistent with our experience with this patient's rapid decline despite maximal efforts to support her aggressively. Eight of the 13 patients (62%) who developed TLS associated with their CRC died secondary to sequelae of their TLS (Table 2).

All but one of the 13 patients had metastatic disease, and 11 of 13 patients had liver metastasis. In all four previously documented cases of spontaneous CRC-associated TLS, liver metastases were present, as was seen in our patient. Our patient's presenting LDH and uric acid were significantly elevated on admission as seen in other reported cases, with the exception of one case which had a normal LDH [14]. The fulminant nature of our patient's presentation was concerning for a possible concurrent lymphoma. This concern was evident in two other cases of spontaneous TLS, with a bone marrow biopsy being pursued in one case [13], and treatment with cyclophosphamide, doxorubicin, and prednisone being used empirically in another [15]. As in our case, coagulopathy was seen in two other cases. Ultimately, treatment was offered in three of the cases of spontaneous TLS, while in one case, the patient was not offered chemotherapy [14]. One difference between our case and most of the other cases of spontaneous CRC-associated TLS was hyper-acute clinical presentation and irreversible multi-organ dysfunction despite aggressive intervention. In the other four cases of spontaneous CRC-associated TLS, only one patient had a similar course, with death within days. However, in the remaining cases, two patients survived their TLS, and aggressive interventions were not taken in another. Overall, in cases when spontaneous tumor lysis occurred in CRC, patient outcomes were poor, with

Table 2 Case-specific characteristics of the 13 patients with CRC-associated TLS

Patient	Spontaneous	Liver metastasis	LDH (U/L)	Uric acid (mg/dL)	TLS outcome	Chemotherapeutic regimen implicated in TLS	Reference
1	Yes	Yes	2304	20.3	Survived	N/A	[12]
2	Yes	Yes	1968	10.4	Survived	N/A	[13]
3	Yes	Yes	226	14.1	Died	N/A	[14]
4	Yes	Yes	NA	NA	Died	N/A	[15]
5	No	Yes	4420	12.4	Survived	FOLFOX	[16]
6	No	No	270	8	Survived	FOLFIRI, cetuximab	[17]
7	No	Yes	541	8	Survived	Cisplatin, etoposide	[18]
8	No	Yes	NA	19.2	Died	Irinotecan	[19]
9	No	Yes	880	12.6	Died	FOLFIRI	[20]
10	No	Yes	3600	30.5	Died	FOLFIRI*	[21]
11	No	No	5014	13.6	Died	FOLFIRI, bevacizumab	[22]
12	No	Yes	59,000	12	Died	Cetuximab	[23]
13	No	Yes	NA	23.1	Died	Regorafenib	[24]
All patients	% spontaneous	% with liver metastasis	Median LDH	Median uric acid	TLS-associated mortality		
	31%	85%	2136	13.1	62%		

FOLFIRI 5-flurouracil,leucovorin, irinotecan, *FOLFOX* 5-flurouracil, leucovorin, oxaliplatin

*Patient also received pelvic irradiation

two of four patients (50%) dying secondary to sequelae of TLS [14, 15]. Our report increases the proportion to 60% (three of five patients in the reported literature).

Intriguingly, our patient's autopsy noted necrosis of liver parenchyma and intrahepatic portal vein thrombosis, which the ultrasound Doppler had failed to detect. However, ultrasound has lower sensitivity in diagnosing portal vein thrombosis compared to MRI and contrast-enhanced CT [25]. Portal vein thrombus and hepatic necrosis were noted in one other case of CRC-related TLS [15]. In that report, there was extensive liver necrosis seen on imaging, which was correlated with findings that occurred during laparotomy. Portal vein thrombus and liver necrosis were not seen in the other cases of CRC-associated TLS. However, in the case of cetuximab-related TLS, there was a significant transaminitis with AST/ALT level of 17,000/3600 [23]. On literature review, we found only four other cases in which a portal vein thrombus was associated with solid tumor TLS [15, 26–29]. In one of the cases, it was hypothesized that the large amount of tumor emboli to the portal venous system and subsequent hepatic necrosis contributed to the development of TLS [27]. In another, there were CT imaging findings suggestive of ischemic hepatitis in the setting of a main portal vein filling defect; however, there was no mention of necrosis [28]. Although there was only one other TLS case report that performed an autopsy [15], the available literature plus our data allows us to speculate that portal vein thrombosis may exacerbate TLS by both increasing cell lysis via ischemia and impairing hepatic function leading to decreased purine metabolism.

We additionally performed an in-depth molecular analysis on this patient's tumor. None of the five mutations we found have been associated with an increased risk of tumor lysis syndrome. Interestingly, while KRAS mutations are common and seen in approximately 40% of CRC [30], HRAS mutations in CRC are quite rare. A single institutional evaluation of the RAS mutational status of 1519 patients with colorectal cancer demonstrated that only 1.7% of patients had an HRAS mutation. In comparison with KRAS-mutant tumors, HRAS mutations are not associated with differences in pretreatment CEA, clinical stage, or 5-year disease-free survival [31]. Moreover, all 26 patients with HRAS mutations had mutations in p.Q61L [31] as compared to the p.Q61K identified in this case. Based on data from the COSMIC somatic mutation database, HRAS mutations occur most frequently in salivary and urinary tract cancers, and are found in < 1% of colorectal cancers [32]. Moreover, no Q61K mutations have yet been reported in colorectal cancer; instead, this point mutation is seen most frequently in thyroid carcinoma [32].

Of the CRC patients who developed TLS secondary to chemotherapy, the most commonly involved drug was irinotecan, which was used as either a single agent or within combination therapy in five of the nine cases of treatment-associated TLS [17, 19–22]. Cetuximab was used in two of the treatment-associated TLS cases [17, 23], while oxaliplatin was involved in one case [16]. Given these small numbers, however, it is not possible to determine if CRC TLS is associated with a specific antineoplastic therapy.

In conclusion, we present a case of spontaneous CRC-associated TLS. TLS is an oncologic emergency which must be identified quickly, and while rare in solitary tumors, its presence is associated with a higher risk of mortality than typically seen with hematologic malignancies. Our patient presented with classic laboratory abnormalities of TLS, with progressive multi-organ dysfunction and ultimately death within days of presentation despite aggressive measures. In most cases of solid tumor-associated TLS, liver metastases are present (85% patients with CRC-associated TLS). Our patient was noted to have portal vein thrombosis, which may have exacerbated her TLS by contributing to extensive liver necrosis. This may suggest that a portal venous thrombosis is an adverse risk factor to consider in CRC (and other solid tumors) TLS. Given that the thrombosis may be tumor thrombus (as in our case), the role of anticoagulation is uncertain. As more effective therapies become available for the treatment of solid tumors, the possibility of TLS must remain on the differential given its potentially devastating sequelae, particularly in patients with a high degree of tumor burden. Future studies should address the role of biomarkers and molecular mutations that are associated with aggressive presentations and increased risk for solid tumor-associated TLS.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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