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# Lurbinectedin-Induced Tumor Lysis Syndrome in Small Cell Neuroendocrine Cancer of the Cecum: A First-Ever Case Report

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Female, 38-year-old  
**Final Diagnosis:** Tumor lysis syndrome  
**Symptoms:** Abdominal pain  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Hematology • Oncology

**Objective:** Unusual clinical course  
**Background:** Lurbinectedin (Lurbi) was first approved in June 2020 for metastatic small cell lung cancer (SCLC) patients with progression following platinum-based chemotherapy. Extrapulmonary small cell neuroendocrine cancers (SCNECs) are treated with regimens used for SCLCs. Tumor lysis syndrome (TLS) in solid SCLCs and SCNECs following Lurbi use has not been reported in the literature so far.

**Case Report:** We report a case of Lurbi-induced TLS in a patient with metastatic SCNEC of the cecum following a single intravenous dose of Lurbi 3.2 mg/m<sup>2</sup>. She presented to the hospital with abdominal pain, anuria, and grade 4 TLS. She required emergent hemodialysis due to acute renal failure. Our patient had a high Ki-67 proliferation index (95%), harbored a huge disease burden, and had bilateral renal metastasis, thus making her more susceptible to develop TLS.

**Conclusions:** Although data regarding the occurrence of TLS due to Lurbi in solid tumors are scarce, it remains a potential complication of Lurbi in neuroendocrine tumors with high proliferation index and large tumor burden.

**Keywords:** Acute Kidney Injury • Carcinoma, Neuroendocrine • Small Cell Lung Carcinoma • Tumor Lysis Syndrome

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## Background

Tumor lysis syndrome (TLS) is one of the most common medical emergencies in patients with cancers. It occurs due to the rapid breakdown of tumor cells and subsequent release of their contents into the bloodstream, usually after starting chemotherapy or spontaneously [1]. TLS is associated with electrolyte abnormalities, including hyperkalemia ( $\geq 6$  mEq/l), hyperuricemia ( $\geq 8$  mg/dl), hyperphosphatemia ( $\geq 4.5$  mg/dl), and hypocalcemia ( $\leq 7$  mg/dl), which eventually cause clinical toxicities in the form of acute kidney failure, seizures, arrhythmias, and death [1,2]. A 25% increase in baseline potassium, uric acid, and phosphate levels and a 25% decrease in baseline calcium level are also considered positive lab indicators for TLS [1,2]. The emergence of newer effective targeted therapies may predispose to tumor breakdown and thus release massive breakdown products, overwhelming the body's homeostasis and disposal mechanisms.

Lurbinectedin (PM01183), a derivative of ecteinascidin, attaches to the DNA minor groove and thus promotes double-strand DNA breaks [3]. The drug is a second-generation analog of trabectedin that suppresses RNA-polymerase-II activity and facilitates its breakdown with the help of ubiquitin/proteasome machinery [3]. Lurbinectedin (Lurbi) was first approved by the Food and Drug Administration (FDA) in June 2020 for metastatic small cell lung cancer (SCLC) patients with disease progression following platinum-based chemotherapy [3]. The approval was based on the evidence from a pivotal phase II basket trial (NCT02454972) that showed an overall response rate of 35% (95%CI: 26.2-45.2) when Lurbi was given as a second-line agent among these patients [4]. Hematological toxicity, elevated creatinine, abnormal liver functions, and fatigue were the most common adverse events (AEs), whereas neutropenia (46%), leukopenia (29%), and thrombocytopenia (7%) were the most common grade (G) 3 or 4 toxicities. Ten percent of patients in this trial had serious toxicity, 5% each accounted for neutropenia and febrile neutropenia. No treatment-related deaths occurred in this trial with 2% discontinuations secondary to toxicity. There were no documented reports of TLS [4]. Extrapulmonary small cell neuroendocrine cancers (SCNECs) are treated with regimens used for SCLCs [5]. This recommendation of parallel treatment paradigms is based on similar histology and biological behavior. TLS due to Lurbi has not been reported so far in solid tumors. We report a patient with metastatic SCNEC of cecum who was treated with Lurbi as third-line therapy and she developed TLS.

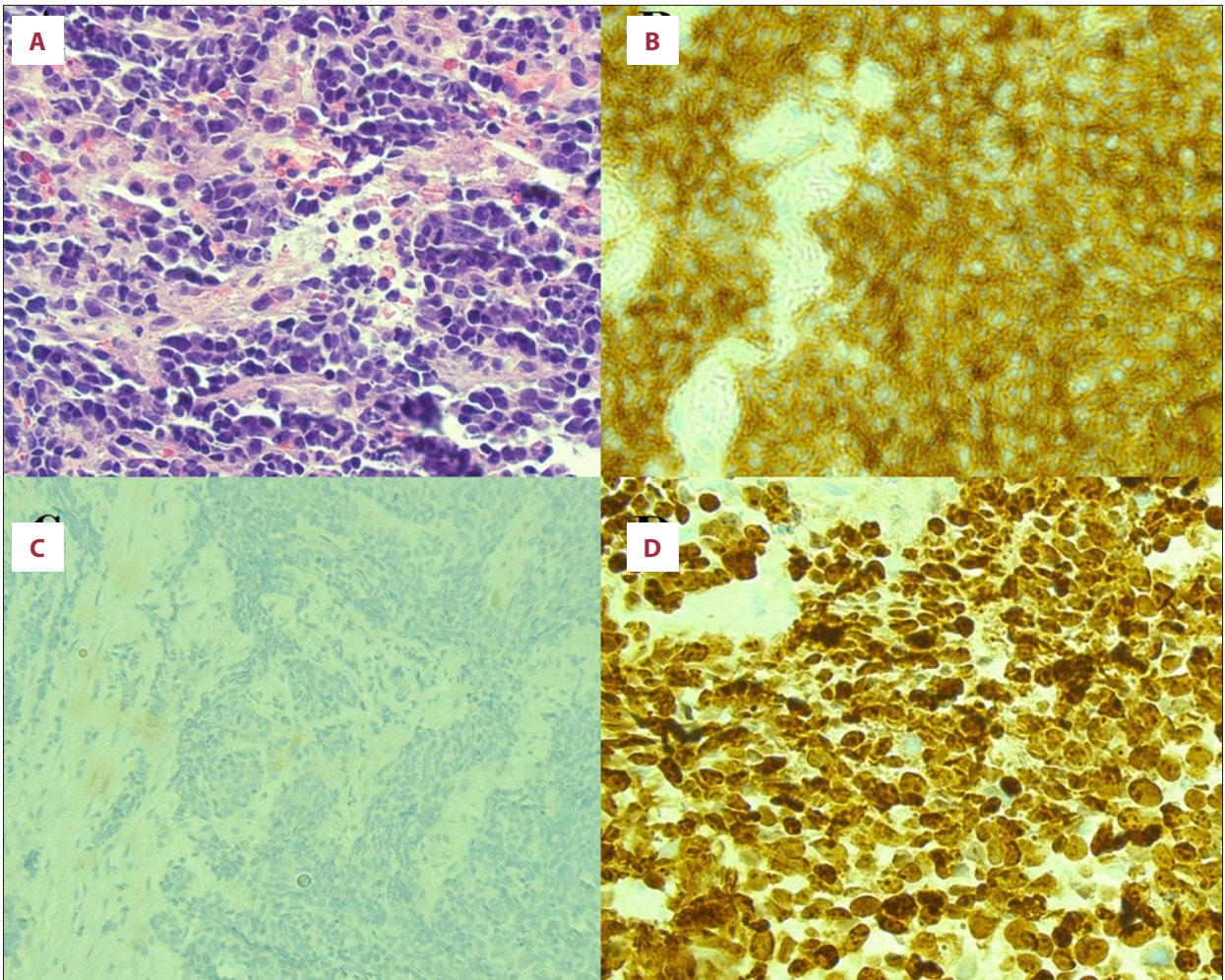
## Case Report

A 38-year-old woman underwent right upper-quadrant ultrasound for abdominal pain, which showed hypoechoic lesions

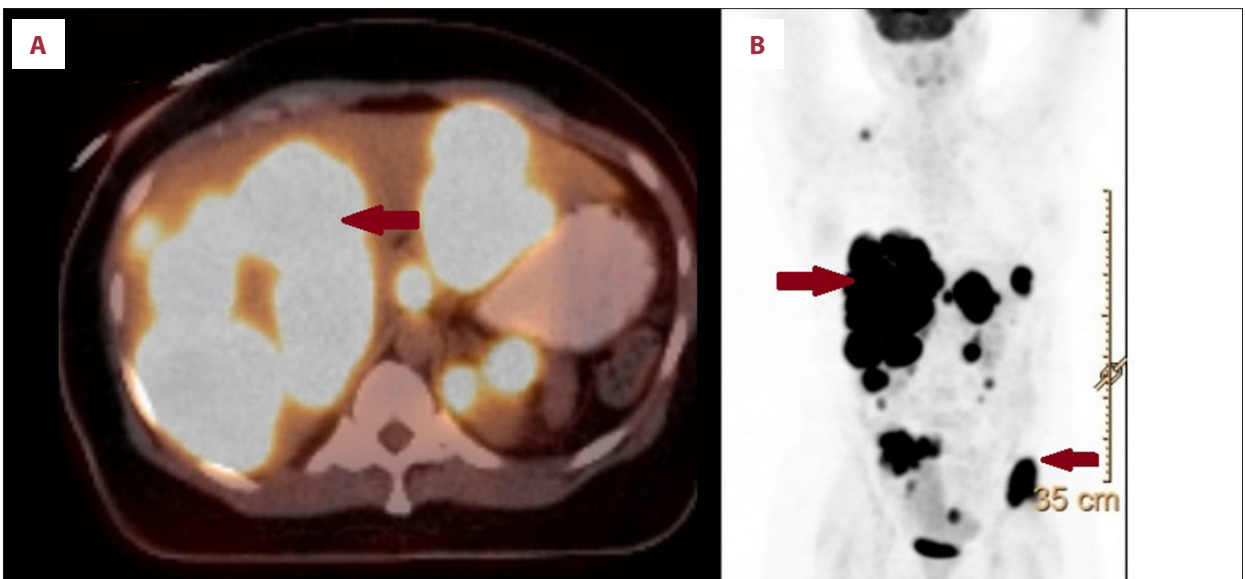
within the liver, concerning for metastasis. The patient did not have a prior history of cancer. She underwent a computed tomography (CT) scan of abdomen with contrast that showed multiple lesions in the liver measuring up to 3.5 cm, concerning for metastatic disease. The patient underwent a chest CT, which showed a normal CT chest. The left adrenal gland had a 1.8-cm nodule, presumably metastatic, and a 2-cm round soft-tissue nodule located in the left kidney and tail of the pancreas, possibly metastatic as well. The patient was also found to have a cecal mass that was thought to be the primary. Magnetic resonance imaging (MRI) of the brain was negative for brain metastasis. She underwent a CT-guided biopsy of the liver. The pathology was consistent with SCNEC of the cecum with Ki-67 greater than 95% (Figure 1). The patient underwent a positron emission tomography (PET) scan (Figure 2), which showed widespread metastasis involving the supraclavicular area, right breast, both kidneys, cecum, the left iliac ala, and the left ovary.

The patient was labelled as metastatic SCNEC with its primary in the cecum. She was started on carboplatin, etoposide, and atezolizumab. The patient underwent a PET scan after 3 cycles of the above-mentioned treatment, which showed reduction in size of most of the lesions. The treatment course was complicated by a partial small-bowel obstruction, which improved following conservative measures. She completed 4 cycles of chemoimmunotherapy followed by 3 cycles of maintenance atezolizumab. Follow-up CT of the chest, abdomen, and pelvis showed worsening of disease in all of the lesions as well as a new left ovarian lesion. MRI of the brain was again negative for metastatic disease.

Next-generation sequencing of the blood showed mutations in APC, KRAS, RB1, and TP53 but no targetable mutations. These mutations are seen in patients with colorectal cancers; therefore, the initial biopsy was re-reviewed with pathology to ensure that we were not dealing with colon cancer with neuroendocrine differentiation, but it was concluded that this was clearly a small-cell neuroendocrine tumor. The decision was made to start the patient on FOLFIRI as second-line therapy given the unavailability of a clinical trial. A follow-up CT scan after 3 cycles of FOLFIRI showed progression of disease in all areas in addition to the development of a large right-sided pleural effusion along with compressive atelectasis. There was a small pathologic nondisplaced fracture of the left iliac crest with increase in the size of the cecal mass. The hepatic disease and lymph nodes were also increased in size. She was started on Lurbi 3.2 mg/m<sup>2</sup> intravenously every 3 weeks as a third-line therapy. The patient received a single dose of Lurbi and was admitted to the hospital 5 days later with abdominal pain. Upon admission, she was noted to be anuric. Lab tests (reference range in parenthesis) performed in the Emergency Department showed blood urea nitrogen 52 mg/dl (70-20),



**Figure 1.** Histopathology of liver biopsy specimen showing (A) hematoxylin and eosin staining and immunohistochemical staining positive for (B) synaptophysin, (C) chromogranin, and (D) Ki-67.



**Figure 2.** (A, B) PET/CT of the patient showing multiple metastatic lesions in liver, right breast, both kidneys, and iliac bone (arrows).

creatinine 3.97 mg/dl (0.60-1.30), eGFR 15 ml/min/1.73 m<sup>2</sup> (>60), sodium 133 mmol/l (135-145), potassium 6.3 mg/dl (3.5-5.5), chloride 100 mmol/l (98-108), and bicarbonate 18 mmol/l (21-32). Phosphorus level was 7.6 mg/dl (2.5-4.9) and uric acid level 19.3 mg/dl. Lactic acid was 4.0 mmol/l (0.4-2.0). AST was 429 IU/L (8-37), ALT 49 IU/L (12-68), ALP 599 IU/L (45-117), total bilirubin 2.3 mg/dl (0.2-1.0), albumin 1.9 mg/dl (3.4-5.0), and total calcium 6.4 mg/dl (8.5-10.1). White blood cell (WBC) count was  $9.89 \times 10^3$ /ul (4.1-10.3), hemoglobin 9.6 gm/dl (11.3-15.3), MCV 69 FL (81-100), MCHC 31 g/dl (32-35), and platelet count  $234 \times 10^6$ /ul (140-400). The patient was diagnosed with TLS secondary to Lurbi. Given her life-threatening electrolyte abnormalities, anuria, and metabolic acidosis, she was initiated on emergent hemodialysis on the same day. After hemodialysis, the lab values improved, with BUN 21 mg/dl, creatinine 1.90 mg/dl, eGFR 36 ml/min/1.73 m<sup>2</sup>, sodium 136 mmol/l, potassium 4.3 mmol/l, chloride 99 mmol/l, bicarbonate 25 mmol/l, and uric acid 7.1 mg/dl. A plan was made to resume hemodialysis based on the patient's renal failure and laboratory profile. However, during the hospitalization, the patient developed pancytopenia (WBC count  $1.1 \times 10^3$ /ul, hemoglobin 7.3 g/dl and platelets  $33 \times 10^6$ /ul) and coagulopathy with elevated PT/INR. The coagulopathy was thought to be due to disseminated intravascular coagulation (DIC) and liver dysfunction. She was given packed RBCs, platelets, FFPs, and IV vitamin K. She was also started on filgrastim. On the following day, the patient developed rectal bleeding. CT abdomen did not identify any source. She was treated with broad-spectrum antibiotics, given her pancytopenia and suspected sepsis. She became hemodynamically unstable, precluding invasive gastrointestinal evaluation. Blood cultures grew *Escherichia coli* and methicillin-sensitive *Staphylococcus aureus*. She continued to deteriorate afterward despite appropriate antibiotics and developed septic shock, requiring multiple pressors. She went into cardiac arrest, requiring CPR and intubation, and she continued to decline. Her family decided to withdraw care given multiorgan failure and dismal prognosis. The patient died 4 days after admission.

## Discussion

Small-cell neuroendocrine cancers (SCNECs) are exceedingly rare tumors of the colon, accounting for 0.6% of all types [6]. They exhibit an aggressive clinical behavior, and two-thirds of them are already metastatic at the time of diagnosis, and thus have a dismal prognosis (median survival: 10.4 months, 95%CI: 6.7-18.9). Chemotherapy is the treatment of choice for metastatic SCNECs. Therefore, we used a platinum-based therapy in our patient due to Ki-67 >55%, as these tumors tend respond well to such therapy [5,7]. However, the patient's tumor burden continued to build up. She also progressed on FOLFIRI and thus had to be started on Lurbi according to

the National Comprehensive Cancer Network (NCCN) guidelines. Following Lurbi, she developed G-4 TLS and acute renal failure and needed emergent hemodialysis.

There are no published reports on the experience and safety regarding the use of Lurbi in SCNECs. Many clinical trials that evaluated the role of Lurbi alone or in combination with other drugs in solid tumors such as SCLC, non-SCLC, sarcoma, metastatic breast cancer, ovarian cancer, malignant mesothelioma, head and neck cancers, and endometrial cancers did not document any event of TLS [4,8-10]. One phase I trial (NCT01970540) evaluated the safety of escalating doses of Lurbi along with doxorubicin in advanced solid tumors, including 9 patients with neuroendocrine cancers [3,8]. There are no reports of TLS in neuroendocrine cancers or any other solid tumor type. One case of TLS was reported in a phase I trial (n=42) that tested various doses of Lurbi ranging from 1 to 7 mg in non-solid tumor type, ie, acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) [11]. One incident of G-4 TLS was reported in a patient with 3 mg of Lurbi, although there were even higher doses given in other patients without developing TLS.

TLS is a function of a multitude of factors (patient-, tumor-, and therapy-related) such as: (1) patient's age and predisposing renal factors, eg, renal insufficiency, dehydration, hyperuricemia, renal invasion of tumor; (2) tumor type (solid vs hematologic) and histology such as acute vs chronic leukemia, Burkitt lymphoma, and neuroblastomas and SCLC; (3) tumor bulkiness, staging and proliferation; (4) tumor sensitivity to chemotherapy; and (5) type of chemotherapy used [12,13]. Patients with hematologic malignancies such as AML and acute lymphoblastic leukemia with WBC count  $\geq 100 \times 10^9$ /l and lactate dehydrogenase level  $\geq 2$  times the upper normal limit are more at risk [12]. Therefore, one TLS case in an AML/MDS patient might be due to such potential factors not documented in the published trial. The co-occurrence of DIC and TLS has been reported in the literature as well, with one acting as a nidus for the other, contributing further to hemodynamic instability [13].

Those solid tumors that have a high proliferation index and show an extreme sensitivity to cytotoxic or targeted drugs may also present with TLS. Our patient had a high Ki-67 proliferation index (95%), harbored a huge disease burden, and had bilateral renal metastasis, thus making her more susceptible to develop TLS. Previously, patients with solid tumors with a high Ki-67 index have been reported to develop TLS [14,15]. Our patient developed abdominal pain from tumor lysis within 5 days of Lurbi and became anuric, along with having metabolite abnormalities. The presentation of such a case demands a proactive prophylactic strategy and high index of suspicion for TLS in neuroendocrine tumors, especially among those that have a high proliferation index. Prophylactic hydration,

diuresis, and hypouricemic agents aiming to improve the urinary flow and prevent renal failure should be instituted. Acute renal failure is an oncological emergency and needs emergent hemodialysis.

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## Conclusions

Although the data regarding the occurrence of TLS due to Lurbi in solid tumors are limited, it remains a potential complication of Lurbi in patients with neuroendocrine tumors with high proliferation index and large tumor burden. Treating physicians should consider TLS as a potential complication of Lurbi and proactively develop a preventive strategy. TLS can be life-threatening, leading to renal failure and death.

## Conflicts of interest

None.