CASE REPORT

Spontaneous tumour lysis syndrome in small cell lung cancer: a rare phenomenon

Prajwal Dhakal,¹ Manoj P Rai,¹ Modina Thrasher,² Mukta Sharma¹¹Internal Medicine, Michigan State University, East Lansing, Michigan, USA²Department of Pathology, Sparrow Hospital, Lansing, Michigan, USACorrespondence to
Dr Manoj P Rai,
manoj.raihc@msu.edu

Accepted 29 May 2018

SUMMARY

Tumour lysis syndrome (TLS) is an oncological emergency. It is caused by cellular death occurring secondary to cancer therapy or spontaneously in rapidly dividing tumours. More common in haematological malignancies, it has also been reported in solid tumours. Out of 14 cases of small cell lung cancer (SCLC) with TLS, only three cases of spontaneous TLS have been reported in literature to date. Here we report a case of SCLC presenting as a spontaneous TLS.

BACKGROUND

Tumour lysis syndrome (TLS) is a life-threatening complication. The incidence and severity of TLS is determined by various factors related to tumour (type of malignancy, stage of tumour and its potential for lysis), patient (patient characteristics) and therapy (type of chemotherapy and supportive therapy during chemotherapy). TLS is more severe in patients with pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine.¹ TLS usually occurs during the initial phase of chemotherapy where tumour cells are rapidly destroyed. However, in rare instances TLS may occur spontaneously before chemotherapy. Even though it is uncommon, spontaneous tumour lysis syndrome (STLS) occurs predominantly in patients with haematological malignancies and is extremely uncommon among patients with solid tumours. As yet, 28 cases of STLS in solid tumours and only three prior cases of small cell carcinoma

Figure 2 CT of chest abdomen and pelvis showing marked hepatomegaly with multiple masses.

of the lung with STLS have been reported. Here we report another case of STLS in a patient, which led to the diagnosis of small cell lung cancer.

CASE PRESENTATION

A man in his early 70s presented to the emergency room with complaints of progressively worsening back spasms for 2 weeks. He described it as severe, non-radiating 10/10 in severity and was reportedly unresponsive to pain medications. His medical history was significant for coronary artery disease, recent non-ST-elevation myocardial infarction, congestive heart failure with reduced ejection fraction and uncontrolled hypertension. Review of systems was positive for fatigue, leg swelling, heartburn, nausea, abdominal pain and decreased urinary output. His temperature was 36.27 C, blood pressure was 119/75 mm Hg, heart rate was 68 beats per minute, respiratory rate of 20 and his oxygen saturation was 97% on room air.

Figure 1 CT of chest abdomen and pelvis showing abnormal tissue in right paratracheal-suprahilar region suggesting bronchogenic carcinoma.

Figure 3 H&E staining of the liver biopsy showing small cell carcinoma (100×).

To cite: Dhakal P, Rai MP, Thrasher M, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224512

Figure 4 H&E staining of the liver biopsy showing small cell carcinoma (400×).

Physical exam was positive for moderate distress due to back pain, 1+ pitting oedema in the lower extremities, diffuse abdominal tenderness and tenderness in the lower back. Lab studies were remarkable for potassium of 7.8 mmol/L, uric acid 17.6 mg/dL, phosphorus of 7.1 mg/dL, alkaline phosphatase 507 U/L, aspartate aminotransferase 171 U/L and alanine transaminase of 78 U/L. Calcium was normal at 10.82 mg/dL. His serum creatinine was 2.4 mg/dL. CT of chest, abdomen and pelvis showed abnormal tissue in right paratracheal-suprahilar region suggestive of bronchogenic carcinoma (figure 1); also, it showed marked hepatomegaly with multiple metastatic lesions (figure 2). In the setting of possible neoplasm, the presence of multiple electrolyte abnormalities (hyperkalaemia and hyperphosphataemia) with hyperuricaemia in the setting of acute kidney injury (AKI) raised the suspicion of STLS. The patient was started on intravenous fluids, one time dose of rasburicase along with daily allopurinol. The patient then developed anuria, and the hyperkalaemia remained refractory to medical management so emergent haemodialysis was performed. The patient remained anuric and continued to be dependent on haemodialysis. Subsequently, liver biopsy showed metastatic small cell neuroendocrine carcinoma (figures 3 and 4). Immunostains were positive for cytokeratin CAM 5.2 (figure 5), cytokeratin AE1/AE3 (figure 6), synaptophysin (figure 7) and CD 36 (figure 8) but negative for chromogranin and P63. Oncology was consulted, and chemotherapy with carboplatin and etoposide was planned.

Figure 5 Immunohistochemical stain positive for cytokeratin CAM 5.2.

Figure 6 Immunohistochemical stain positive for cytokeratin AE1/AE3.

OUTCOME AND FOLLOW-UP

However, before any chemotherapy could be started, patient developed encephalopathy with visual hallucinations and had bright red blood per rectum along with cyanosis and mottling of abdomen and extremities. Despite aggressive measures, the patient deteriorated rapidly and passed away.

DISCUSSION

To date, 14 cases of TLS among patients with small cell carcinoma have been reported in literature (table 1).^{2–15} There was equal gender distribution with 50% males (n=7) and females (n=7).^{2 6 10–14} Most of the patients who developed TLS had advanced disease and except for one case, which was limited stage.¹⁴ Among the 14 patients with TLS, 3 of them presented with spontaneous TLS^{12 13 15}; chemotherapy was determined to be the cause of TLS in remaining 11 patients. Seven of them received a combination of cisplatin and etoposide. The rest of them received other regimens (1: doxorubicin, etoposide and cisplatin; 1: doxorubicin, cyclophosphamide and vincristine; 1: intravenous topotecan; 1: unknown). Our patient was planned for chemotherapy with carboplatin and etoposide, but he passed away before it could be initiated.

TLS has been classified by Cairo *et al*¹⁶ into two types: laboratory and clinical TLS. Laboratory TLS is defined as the presence of hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia within 3 days before or up to 7 days after starting chemotherapy is defined as laboratory TLS. Elevated creatinine level, seizures, dysrhythmia or death along with fulfilment of criteria for laboratory TLS is required for clinical TLS.¹⁶ Howard *et al*¹ redefined TLS and proposed that the presence of 2 concomitant metabolic abnormalities is necessary for TLS diagnosis and a raise by 25% from baseline should be considered a criterion only in cases with its levels above normal limits. Also, he proposed that a symptomatic hypocalcaemia should constitute clinical TLS.

Figure 7 Immunohistochemical stain positive for synaptophysin.

Figure 8 Immunohistochemical stain positive for CD 36.

Nucleic acids released during tumour lysis is metabolised into hypoxanthine, then into xanthine, and finally into uric acid.¹⁷ Potassium and phosphorus are also released with cell lysis. Severe hyperkalaemia carries the risk of causing fatal dysrhythmias. Hyperphosphataemia can cause hypocalcaemia, and severe hypocalcaemia may cause neuromuscular irritability, seizures and dysrhythmia. Similarly, precipitation of calcium phosphate crystals or uric acid in kidneys can lead to AKI.¹⁸ Uric acid has the potential to reduce renal flow by causing renal vasoconstriction and can also cause inflammatory changes.^{19–21} Cytokines released during tumour lysis can often cause systemic inflammatory

response syndrome and multiorgan failure.^{22–24} Our patient had lab abnormalities typical for TLS such as hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia.

In cases of TLS, promotion of diuresis and increasing hydration has been shown to confer superior renal protection against urate nephropathy compared with acetazolamide and bicarbonate.²⁵ Allopurinol and recently rasburicase are being used to preserve or improve renal function in patients with TLS.²⁶ Allopurinol, a purine analogue, acts by inhibiting xanthine oxidase (figure 9). However, rasburicase acts by catalysing oxidation of uric acid to allantoin, which is an inactive, more soluble substrate.²⁶ The incidence of TLS and the need for dialysis have been found to be lower among patients on rasburicase than those on allopurinol.^{27 28} Urinary alkalinisation is outdated and is not used for management of TLS currently, because it reduces the solubility of calcium, leading to calcium deposition and subsequent renal failure. Among patients with TLS the threshold for dialysis or renal replacement therapy is lower, oliguria causing refractory hyperkalaemia and symptomatic hypocalcaemia secondary to hyperphosphataemia require haemodialysis.¹ Continuous renal-replacement therapy (CRRT) is advocated instead of regular haemodialysis in the setting of TLS, because phosphate is clearly more efficient with CRRT compared with haemodialysis.²⁹ Our patient was managed with daily allopurinol after one time dose of rasburicase. Haemodialysis was performed in our patient since hyperkalaemia was not responsive to medical management.

Table 1 Previously reported cases of small cell lung cancer with tumour lysis syndrome^{2–15}

Author	Age (year), sex	Diagnosis	Chemotherapy used	Presenting features of TLS	Management	Outcome	Cause of death
Vogelzang <i>et al</i> ²	57, F	Small cell bronchogenic carcinoma	Doxorubicin, etoposide and cisplatin.	Hyperkalaemia, azotaemia and hypocalcaemia.	Aggressive hydration.	Dead	Cardiac arrest
Baumann <i>et al</i> ³	78, M	SCLC	Doxorubicin, cyclophosphamide and vincristine.	Hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Aggressive hydration, allopurinol and urinary alkalinisation.	Not applicable	Not applicable
Hussein and Feun ⁴	Not known	SCLC	Cisplatin and etoposide.	Not mentioned.	Not applicable.	Not applicable	Not applicable
Ohnishi <i>et al</i> ⁵	67, M	SCLC	Cisplatin and etoposide.	Hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Allopurinol, aggressive hydration and sodium bicarbonate.	Not applicable	Not applicable
Kalemkerian <i>et al</i> ⁶	74, F	SCLC	Cisplatin and etoposide.	Hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Aggressive hydration, sodium bicarbonate infusion, followed by forced diuresis.	Not applicable	Not applicable
Marinella ⁷	Not known	SCLC	Cisplatin and etoposide.	Not mentioned.	Not mentioned.	Not applicable	Not applicable
Heching ⁸	NA	SCLC (metastatic)	Not mentioned	Not mentioned.	Not mentioned.	Not applicable	Not applicable
Kallab and Jillella ⁹	61, M	SCLC	Cisplatin and etoposide.	Hyperkalaemia, hyperphosphataemia and hyperuricaemia.	Aggressive hydration.	Death	Not applicable
Beriwal <i>et al</i> ¹⁰	68, F	SCLC (extensive)	Intravenous topotecan.	Hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Aggressive hydration.	Dead	Disseminated intravascular coagulation and multiorgan failure.
Mott <i>et al</i> ¹¹	Not mentioned	SCLC	Cisplatin and etoposide.	Not known.	Aggressive hydration and allopurinol.	Not applicable	Not applicable
Jallad <i>et al</i> ¹²	75, F	SCLC (poorly differentiated)	No chemotherapy.	Hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Patient refused interventions including haemodialysis.	Dead	Not applicable
Padhi and Singh <i>et al</i> ¹³	73, F	SCLC	No chemotherapy.	Hyperphosphataemia, hyperuricaemia and hypocalcaemia.	Aggressive hydration.	Dead	Acute respiratory failure secondary to bronchial obstruction.
Boikos ¹⁴	70, F	SCLC (limited stage)	Cisplatin and etoposide.	Hypocalcaemia, hyperphosphataemia and hyperuricaemia.	Aggressive hydration, allopurinol and rasburicase.	Not applicable	Not applicable
Kanchustambham <i>et al</i> ¹⁵	53, M	SCLC	No chemotherapy.	Hyperkalaemia, hyperphosphataemia and hyperuricaemia.	Aggressive hydration, allopurinol and rasburicase.	Alive	—

SCLC, small cell lung cancer; TLS, tumour lysis syndrome.

Pathophysiology of tumour lysis syndrome²

Figure 9 Pathophysiology of tumour lysis syndrome (minor modification from Howard *et al.*¹ Tumour cell lysis leads to release of large amounts of nucleic acids along with potassium and phosphate into the systemic circulation. Nucleic acids are catabolised to uric acid causing hyperuricaemia, which can precipitate in the renal tubules and cause acute kidney injury. Allopurinol acts by inhibiting xanthine oxidase; thus, it blocks metabolism of hypoxanthine and xanthine to uric acid. Rasburicase acts by promoting degradation of uric acid by catalysing the oxidation of uric acid to allantoin, which is relatively more water soluble.

For patients with active TLS, transfer to the critical care for continuous cardiac monitoring and laboratory monitoring every 4–6 hours is recommended. Critical care transfer is also recommended for patients at high risk for tumour lysis. Our patient was managed in critical care setting with regular cardiac and laboratory monitoring. Laboratory monitoring can be restricted to a frequency

of every 8–12 hours in patients with intermediate risk and to daily basis in patients with low risk.¹ Strict input and output is also recommended for all patients with TLS.¹

To conclude, STLS is a rare phenomenon in SCLS. Anecdotally, patients with extensive metastasis are the ones who are at greater risk for STLS. Additionally, tumour-related and patient-related factors alter the risk of STLS.

Contributors PD wrote the case description, discussion and revised the manuscript. MPR contributed to the introduction, discussion and learning points. MT provided description on the pathology slides. MS revised the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med* 2011;364:1844–54.
- Vogelzang NJ, Nelmark RA, Nath KA. Tumor lysis syndrome after induction chemotherapy of small-cell bronchogenic carcinoma. *JAMA* 1983;249:513–4.
- Baumann MA, Frick JC, Holoye PY. The tumor lysis syndrome. *JAMA* 1983;250:615.
- Hussein AM, Feun LG. Tumor lysis syndrome after induction chemotherapy in small-cell lung carcinoma. *Am J Clin Oncol* 1990;13:10–13.
- Ohnishi T, Mori K, Ohta S, *et al.* Tumor lysis syndrome in widely metastatic small-cell lung cancer. *Int J Clin Oncol* 1997;2:235–7.
- Kalemkerian GP, Darwish B, Varterasian ML. Tumor lysis syndrome in small cell carcinoma and other solid tumors. *Am J Med* 1997;103:363–7.
- Marinella MA. Fatal tumor lysis syndrome and gastric hemorrhage associated with metastatic small-cell lung carcinoma. *Med Pediatr Oncol* 1999;32:464–5.
- Heching BN. Tumor lysis syndrome in metastatic small-cell cancer. *Proceedings ODAACR* 1988;29:179.
- Kallab AM, Jillella AP. Tumor lysis syndrome in small cell lung cancer. *Med Oncol* 2001;18:149–52.
- Beriwal S, Singh S, Garcia-Young JA. Tumor lysis syndrome in extensive-stage small-cell lung cancer. *Am J Clin Oncol* 2002;25:474–5.
- Mott FE, Esana A, Chakmakjian C, *et al.* Tumor lysis syndrome in solid tumors. *Support Cancer Ther* 2005;2:188–91.
- Jallad B, Hamdi T, Latta S, *et al.* Tumor lysis syndrome in small cell lung cancer: a case report and review of the literature. *Onkologie* 2011;34:129–31.
- Padhi P, Singh S. Spontaneous tumor lysis syndrome in a patient with metastatic small cell carcinoma of the lung. *J Cancer Sci Ther* 2012;04.
- Boikos SA, Forde PM, Chatterjee S, *et al.* Tumor lysis syndrome in limited-stage small-cell lung cancer. *J Thorac Oncol* 2013;8:e61–2.
- Kanchustambham V, Saladi S, Patolia S, *et al.* Spontaneous tumor lysis syndrome in small cell lung cancer. *Cureus* 2017;9:e1017.
- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127:3–11.
- Hochberg J, Cairo MS. Rasburicase: future directions in tumor lysis management. *Expert Opin Biol Ther* 2008;8:1595–604.
- Howard SC, Ribeiro RC, Pui C-H. Acute complications. *Childhood Leukemias*:709–49.
- Ejaz AA, Mu W, Kang DH, *et al.* Could uric acid have a role in acute renal failure? *Clin J Am Soc Nephrol* 2007;2:16–21.
- Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811–21.
- Shimada M, Johnson RJ, May WS, *et al.* A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. *Nephrol Dial Transplant* 2009;24:2960–4.
- Hijiya N, Metzger ML, Pounds S, *et al.* Severe cardiopulmonary complications consistent with systemic inflammatory response syndrome caused by leukemia cell lysis in childhood acute myelomonocytic or monocytic leukemia. *Pediatr Blood Cancer* 2005;44:63–9.
- Nakamura M, Oda S, Sadahiro T, *et al.* The role of hypercytokinemia in the pathophysiology of tumor lysis syndrome (TLS) and the treatment with continuous hemodiafiltration using a ... and Apheresis Science [Internet]. 2009 <http://www.sciencedirect.com/science/article/pii/S1473050208001717>
- Soares M, Feres GA, Salluh JI. Systemic inflammatory response syndrome and multiple organ dysfunction in patients with acute tumor lysis syndrome. *Clinics* 2009;64:479–81.
- Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. *J Clin Invest* 1977;59:786–93.

Learning points

- Typically, tumour lysis syndrome (TLS) occurs with the initiation of chemotherapy due to accelerated cell turnover; however, in rare instance, it can occur spontaneously even before starting chemotherapy.
- Although rare, spontaneous tumour lysis can occur in patients with small cell lung cancer, specially in patients with metastatic disease.
- Aggressive hydration, diuresis, allopurinol or rasburicase can be helpful in prevention of TLS. However, in rare cases, patient may develop severe acute kidney injury requiring haemodialysis.

- 26 Pui CH, Mahmoud HH, Wiley JM, *et al*. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients With leukemia or lymphoma. *J Clin Oncol* 2001;19:697–704.
- 27 Goldman SC, Holcenberg JS, Finklestein JZ, *et al*. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001;97:2998–3003.
- 28 Cairo MS, Gerrard M, Sposto R, *et al*. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood* 2007;109:2736–43.
- 29 Tan HK, Bellomo R, M'Pis DA, *et al*. Phosphatemic control during acute renal failure: intermittent hemodialysis versus continuous hemodiafiltration. *Int J Artif Organs* 2001;24:186–91.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow