CASE REPORT

Spontaneous tumour lysis syndrome associated with contrast dye iohexol use in mantle cell lymphoma

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SUMMARY

We describe a case of a 73-year-old man who presented with right-sided abdominal pain associated with palpable mass. Initial laboratory examination was normal except lactate dehydrogenase level. Subsequent CT image showed situs inversus and splenic mass with multiple lymph nodes enlargement. Biopsy taken from the splenic mass demonstrated mantle cell lymphoma. Staging CT examination was performed with intravenous contrast, and patient developed altered mental status, respiratory failure and acute kidney injury requiring intensive care unit care. Laboratory examination revealed hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia, which are consistent with spontaneous tumour lysis syndrome. The patient was successfully treated with rasburicase and haemodialysis, and completed the first course of chemotherapy without further complications.

BACKGROUND

Tumour lysis syndrome (TLS) is one of the medical emergencies in patients with aggressive tumours and high tumour burden. Cancer cells dying on chemotherapy or radiotherapy release significant amounts of nucleic acids, proteins and electrolytes into the extracellular system causing electrolyte imbalance including hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia which lead to multiorgan failure affecting renal, musculoskeletal and nervous systems.[1–5] However, in rare cases, patients with cancer can develop spontaneous TLS prior to chemotherapy.[6–9] Although the mechanisms of spontaneous TLS remain elusive, studies have shown several risk factors such as pre-existing renal impairment, exposure to nephrotoxins and elevated lactate dehydrogenase (LDH) level.[10 11] Cancer cells constantly undergo proliferation and cell death with higher turnover rates compared to normal cells, and an elevated LDH level in the circulation reflects ongoing tumour lysis.[12–14] In these patients, early recognition and intervention of spontaneous TLS before progression to overt TLS are essential for better clinical outcomes. We present a case of a male patient with mantle cell lymphoma (MCL), who presented with spontaneous tumour lysis, and later developed spontaneous TLS on intravenous contrast dye exposure.

CASE PRESENTATION

A 73-year-old man presented with sudden onset right-sided abdominal pain which developed 4 days prior to admission. The pain was sharp, intermittent and located in the right upper quadrant. It was alleviated with physical activity, and associated with nausea, shortness of breath and abdominal fullness. Vital signs revealed a blood pressure of 109/63 mm Hg, heart rate 96 bpm, respiratory rate 20 breaths/min and temperature 36.2°C. Physical examination was remarkable for a 4 cm×4 cm palpable mass in the right upper quadrant with local tenderness. Murphy's sign was negative. There were no signs of obstructive jaundice and no cervical, supraclavicular, axillary or inguinal lymphadenopathy was palpable.

Pertinent laboratory examination revealed serum sodium 136 (normal 136–145 mmol/L), potassium 4.5 (normal 3.4–5.1 mmol/L), chloride 98 (normal 98–107 mmol/L), bicarbonate 27 (normal 22–29 mmol/L), blood urea nitrogen (BUN) 14 (normal 8–23 mg/dL), creatinine 0.7 (normal 0.67–1.17 mg/dL), calcium 9.4 (normal 8.8–10.2 mg/dL) (corrected calcium 9.64 mg/dL), phosphorus 4.5 (normal 2.7–4.9 mg/dL) and uric acid 6.4 (normal 3.5–8.2 mg/dL) with no signs of acute kidney injury; however, elevated LDH of 766 (normal 135–225 U/L) was noted (table 1). Complete blood count showed white cell count 9.8 K/μL, haemoglobin 15.0 g/dL, haematocrit 44.5%, and platelet 177 K/μL.

Subsequent CT scan of the abdomen and pelvis with contrast demonstrated situs inversus, multiple splenic masses on the right side, and lymph node enlargement in the paracaval area as well as porta hepatis (figure 1). CT-guided biopsy and multiple staging CT scans with intravenous contrast were performed concerning malignancy. However, 7 h after CT examination, the patient developed respiratory failure with O_2 saturation of 70%, oliguria with urine output less than 10 mL/h, hypotension and loss of consciousness. Arterial blood gas showed pH 7.15, $PaCO_2$ 86 mm Hg, PaO_2 67 mm Hg, bicarbonate 27 mmol/L, and serum chemistry revealed LDH 502 U/L, uric acid 17.3 mg/dL, phosphorus 5.8 mg/dL, calcium 7.6 mg/dL, potassium 6.7 mmol/L, BUN 61 mg/dL and creatinine 3.7 mg/dL, which are consistent with acute renal failure and spontaneous TLS meeting Cairo-Bishop definition[15] (table 1).

TREATMENT

The patient was transferred to the intensive care unit (ICU) and intubated for the respiratory failure. Also, rasburicase was given immediately in order to lower the level of uric acid, and haemodialysis was initiated to correct electrolyte imbalance. Over the next couple of days, serum electrolytes were

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Table 1 Laboratory values during the hospital course

Labs	Day 1	Day 5	Day 6	Day 7	Day 8	Day 12	Reference range
LDH	766	502	498	518	526	355	135–225 U/L
Uric acid	6.4	17.3	5.5	3.0	4.4	4.5	3.5–8.2 mg/dL
Phosphorus	4.5	5.8	3.9	4.0	4.4	N/A	2.7–4.9 mg/dL
Potassium	4.5	6.7	5.4	4.0	3.9	3.8	3.4–5.1 mmol/L
Calcium	9.4	7.6	7.3	7.7	7.9	9.0	8.8–10.2 mg/dL
BUN	14	61	50	68	97	63	8–23 mg/dL
Creatinine	0.7	3.7	2.8	2.4	2.2	1.1	0.67–1.17 mg/dL

BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

normalised and urine output improved. Other possible causes of acute renal failure including dehydration, obstructive uropathy and acute glomerulonephritis were reviewed; however, the initially elevated LDH, development of electrolyte imbalance after multiple exposures to intravenous contrast dye, iohexol, as well as clinical improvement with rasburicase and haemodialysis suggest the diagnosis of spontaneous tumour lysis that progressed to overt TLS by temporary renal impairment on contrast dye exposure.

OUTCOME AND FOLLOW-UP

CT-guided biopsy taken from the splenic mass confirmed the diagnosis of MCL with positive CCND1/IGH gene rearrangement (figure 2). Microscopic examination demonstrated a monomorphic population of large atypical cells, which have high N:C ratio, prominent nucleoli as well as scattered mitotic figures with background tumour necrosis. Subsequent immunohistochemistry staining demonstrated atypical cells positive for CD20, cyclin D1 and Bcl-2 with Ki-67 of 70%; however, negative for CD3, CD43, CD30, CD10, CD5, ALK-1, cytokeratin, synaptophysin and chromogranin. After completion of the first cycle of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy with allopurinol to prevent recurrence of tumour lysis syndrome, patient was discharged without further complication and with plans for chemotherapy on an outpatient basis.

DISCUSSION

TLS is an oncological emergency, which is caused by the release of electrolytes and nucleotides into the extracellular system when tumour cells undergo cell death.[1] Nucleic acids are converted into uric acid leading to hyperuricaemia, which subsequently induces acute kidney injury. The mechanism of acute kidney injury includes uric acid and calcium phosphate deposition in the renal tubules causing renal vasoconstriction and decrease of renal flow.[1 10] TLS usually develops with chemotherapy or radiotherapy in patients with aggressive tumours. Examples of high-risk group (>5% risk of TLS) among others are Burkitt leukaemia, Burkitt lymphoma with stage III or higher and acute lymphocytic leukaemia with leukocytosis that are known as aggressive tumours.[15 16]

The Cairo-Bishop criteria was proposed for the diagnosis of laboratory and clinical TLS in 2004 (table 2).[15] Spontaneous TLS is a very rare form of TLS, and it is defined as spontaneous acute kidney injury associated with hyperuricaemia prior to chemotherapy or radiotherapy. Spontaneous TLS usually develops in cancers with a high proliferation rate,[10 15] and its risk factors are categorised into tumour-related intrinsic and host-related extrinsic factors. High rate of proliferation reflected

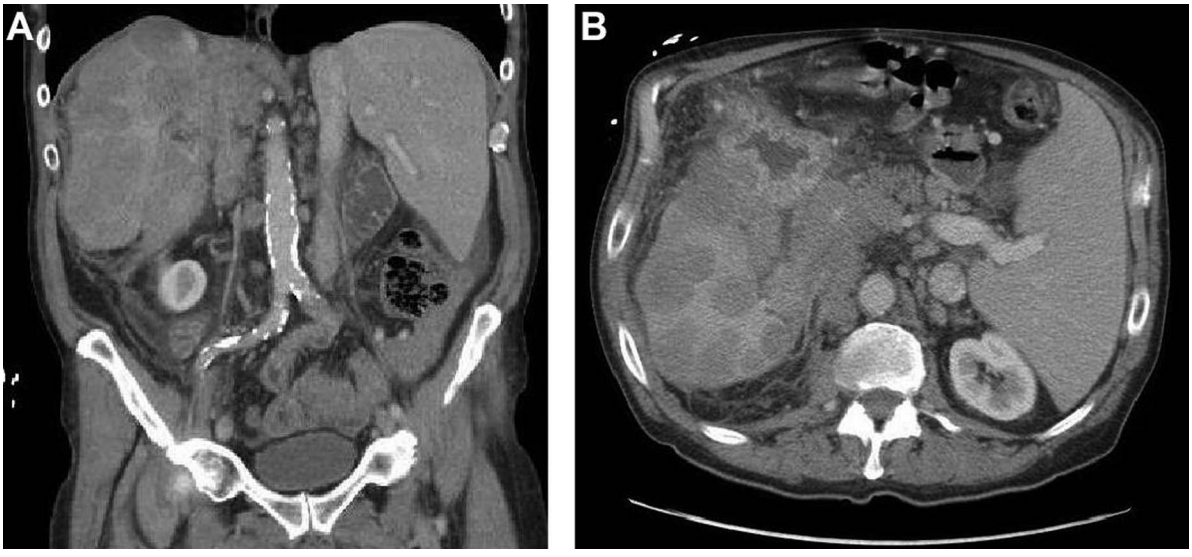

Figure 1 CT of the abdomen and pelvis with contrast dye showing situs inversus and 8 cm×6.9 cm mass in splenic hilus. Multiple masses are observed in spleen, and the largest one measures 4.8 cm centrally, and 5.8 cm superiorly and anteriorly. Multiple lymph nodes enlargements are observed in paracaval area as well as porta hepatis.

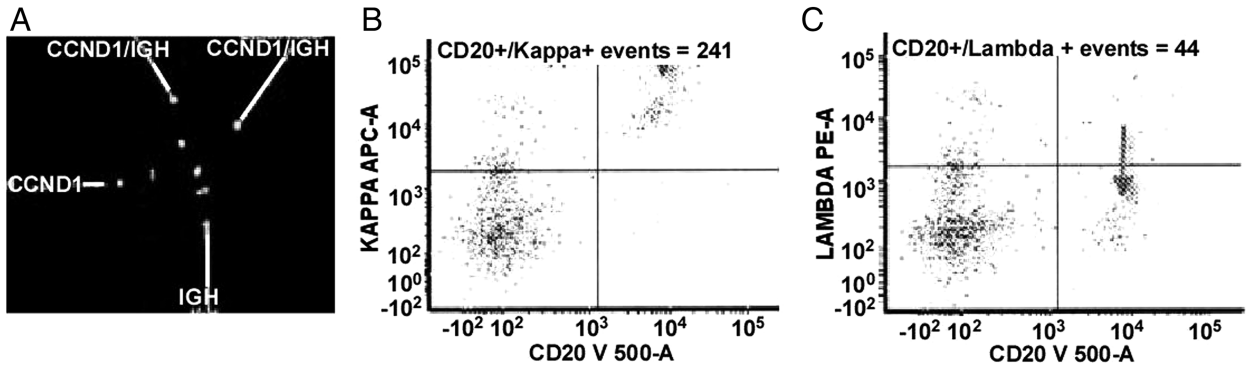

Figure 2 Fluorescence in situ hybridisation (FISH) and flow cytometry. Translocation (11;14) results in the fusion of the cyclin D1 gene (CCND1) (also known as BCL1) at 11q13 with the immunoglobulin heavy chain gene (IgH) at 14q32. FISH analysis was performed with cells from splenic mass using DNA probes for CCND1/IGH. Two hundred interphase nuclei were examined, and 85% of cells were positive for CCND1/IGH rearrangement (A). About 0.8% of total cells and 10.6% of lymphoid cells are B cells with monotypic expression of κ light chains. The monotypic B cells have CD19, CD20, CD5 (–), CD10 (–), CD23 (–), FMC7 (+) (B).

in a high Ki-67 score, chemosensitivity or radiation sensitivity, high tumour burden defined as bulky lesion >10 cm in diameter, leukocytosis >50 000/μL, LDH two times higher than the upper limit of normal value and bone marrow infiltration are well known tumour-related intrinsic factors. MCL is typically classified as a low-risk group for TLS along with small lymphocytic, follicular, marginal zone B-cell, cutaneous T-cell lymphomas based on risk assessment by malignant disease type,[16] although its rare variant, blastoid variant (BV) MCL, is known as a highly aggressive subtype with poor prognosis.[17] In our patient, histological examination and molecular analysis confirmed the diagnosis of typical, non-blastoid MCL. However he had multiple intrinsic risk factors including Ki-67 of 70%, bulky lesions in the spleen and LDH higher than twice of the normal limit, predisposing to the development of spontaneous TLS.

Host-related extrinsic factors play an important role in TLS as well. Uric acid >7.5 mg/dL, underlying renal dysfunction with creatinine >1.5 mg/dL, volume depletion, and exposure to contrast dye are good examples of host-related extrinsic risk factors[11 16 18] Aggressive tumours with a high turnover rate undergo spontaneous cell death and proliferation releasing LDH into circulation. Therefore, LDH is a direct marker of tumour lysis as well as a risk factor of TLS.[13 14 19] In the setting of spontaneous tumour lysis, electrolyte levels can stay within normal range until the development of overt TLS, although the mechanism remains elusive. Two different hypotheses have been suggested: the reabsorption of electrolytes released from necrotising cells into adjacent proliferating cells[20] and the compensation of electrolyte imbalances through renal clearance.[11 16] The safety margin in patients with a high tumour burden is relatively narrow and the renal function can be rapidly affected by nephrotoxic agents as in this case.[21–24] On presentation, the majority of electrolytes were normal except an elevated LDH suggesting ongoing spontaneous tumour lysis and then the patient developed spontaneous TLS after the use of intravenous contrast dye, which likely caused temporary renal impairment that potentiated TLS. Moreover, Naranjo adverse drug reaction probability score of iohexol is 7 in this case, further supporting the claim that spontaneous TLS was potentiated by intravenous contrast dye exposure.[25]

Prophylaxis plays a pivotal role in the management of TLS, and the prophylactic managements are different depending on the risk stratification as discussed in the previous paragraphs.[16 19] For the high risk patients, aggressive intravenous hydration with prophylactic rasburicase rather than allopurinol is recommended unless patients have contraindication for large amounts of fluid, because allopurinol only blocks the new production of uric acid without affecting the one already existing in the circulation.[16] However, for the intermediate group, prophylactic allopurinol rather than rasburicase is recommended in the absence of hyperuricaemia.[18 26–28] Allopurinol is cleared through renal system, and it can cause xanthine nephropathy. As such, careful monitoring of urine output is important.[29] Once TLS develops, there is little benefit from rasburicase or allopurinol, and haemodialysis is the most effective modality to correct electrolyte imbalance and rapidly remove uric acid from the circulation.[15]

The patient in this case was not receiving any prophylactic treatment for TLS due to the lack of a pathology report indicative of an aggressive haematological malignancy, no electrolyte abnormality and normal renal function on initial presentation, and underestimation of the value of elevated LDH level. Consequently, the patient had to be transferred to the ICU for the management of multiorgan failure associated with TLS, and this could have been prevented if risk of spontaneous tumour lysis was recognised earlier and prophylactic management was initiated properly. In conclusion, careful attention to the intrinsic and extrinsic risk factors is important for the prevention of TLS, especially in patients with aggressive cancers or with high tumour burden.

Patient was admitted on day 1. CT of the head and chest with contrast were performed on day 4, and the patient was transferred to ICU on day 5. Patient underwent multiple courses of

Table 2 Cairo-Bishop definition of tumour lysis syndrome

Laboratory TLS	Clinical TLS		
Labs	Values	Changes from baseline	Clinical complication
Uric acid	≥8 mg/dL	25% increase	Creatinine >1.5 times of UNL
Phosphorus	≥4.5 (adult) or ≥6.5 mg/dL (child)	25% increase	Cardiac arrhythmic
Calcium	≤7 mg/dL	25% decrease	Sudden cardiac death
Potassium	≥6 mmol/L	25% increase	Seizure

UNL, upper normal limit.

haemodialysis including days 5, 6 and 8. First course of R-CHOP chemotherapy was initiated on day 7.

Laboratory TLS is defined as ≥2. Laboratory values changes within 3 days before and 5 days after chemotherapy or radiotherapy, clinical TLS is defined as laboratory TLS and at least one of the clinical complications.[15]

Learning points

- Tumour lysis syndrome is an oncologic emergency, and requires careful attention and early detection in patients with aggressive tumour or high tumour burden.
- Spontaneous tumour lysis can occur before chemotherapy, and electrolytes including uric acid, potassium, calcium and phosphorus might be normal.
- Spontaneous tumour lysis can be precipitated by nephrotoxic agents, and early initiation of prophylactic treatment is pivotal to prevent future complications.

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