CASE REPORT

Management of tumour lysis syndrome during first-line palliative chemotherapy for high-volume colorectal cancer

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SUMMARY

Tumour lysis syndrome (TLS) is a rare oncological emergency in solid tumours. Because it is associated with bad short-term prognosis, early recognition and treatment are mandatory. This case refers to a middle-aged woman who presented with stage IV colon cancer, with massive hepatic involvement. After three cycles of first-line FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin), she developed acute kidney injury and hyperkalaemia that did not respond to standard measures. High suspicion of TLS prompted further corroborating investigations and early intensive care unit admission. With vigorous hydration and allopurinol, TLS completely resolved and the patient was discharged. Prophylaxis of subsequent TLS recurrence was complicated by biopsy-proven neutrophilic vasculitis secondary to allopurinol. Prevention of TLS with hydration and rasburicase was performed prior to each subsequent cycle of chemotherapy. This case report is intended to highlight risk factors for TLS in solid tumours and focus on treatment and secondary prophylaxis of TLS.

BACKGROUND

Tumour lysis syndrome (TLS) is an oncological emergency which is rarely encountered in solid tumours. It is estimated that adult solid tumours and their paediatric counterparts account for 1% and 5% of all TLS cases, respectively.¹ However, incidence of TLS in these tumours is unknown.²

TLS is characterised by massive tumour cell lysis with release of large amounts of intracellular electrolytes and metabolites into the bloodstream. It frequently occurs after the beginning of anti-neoplastic treatments but may also occur spontaneously. Once the presence of such metabolites exceeds their renal clearance threshold, hyperuricaemia, hyperkalaemia, hyperphosphataemia and secondary hypocalcaemia develop (laboratory TLS). These, in turn, lead to crystal nephropathy, acute kidney injury (AKI), cardiac arrhythmias or seizures and may result in patient's death (clinical TLS). Mortality of TLS in solid tumours can be as high as 35%,³ which is surprisingly higher than TLS mortality in haematological malignancies (1.9%).⁴

Primary prophylaxis of TLS has been established in international guidelines.⁵ Most solid tumours are classified as low-risk cancers for developing TLS and should undergo routine prophylactic hydration and laboratorial monitoring only. However, some

patients may be at increased risk of developing TLS due to: (1) disease-related factors: highly proliferative, bulky or chemosensitive tumours, such as extensive stage small cell lung cancers, germ cell tumours and paediatric medulloblastomas and neuroblastomas and (2) patient-related factors: age, baseline kidney dysfunction, elevated serum lactate dehydrogenase (LDH) and uric acid levels.⁶ In those cases, patients should be considered for further preventive measures such as use of uricolytic agents (allopurinol or rasburicase). While TLS prophylaxis is considered a cost-effective intervention,⁷ the scarcity of evidence in solid tumours hinders improvement in TLS outcomes.

This case report exemplifies the occurrence of TLS during treatment of a highly prevalent metastatic cancer. Very few cases of TLS have been described following treatment of colon cancer with FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin).^{8,9} It clearly reflects how early diagnosis and treatment improve patient outcomes. It also sheds light on the feasibility of secondary TLS prophylaxis, of which there are very little data.

CASE PRESENTATION

This case relates to a 51-year-old woman who had a history of controlled arterial hypertension and grade 2 obesity, who was medicated with an angiotensin receptor blocker/calcium channel antagonist combination and a thiazide diuretic. She was a non-smoker, had occasional mild alcohol consumption and denied any history of illicit drug abuse. She had no family history of cancer.

She had recently been diagnosed with stage IV adenocarcinoma of the left colon, following initial work-up for upper right abdominal pain: CT scan had revealed an enlarged liver with diffuse hepatic metastases (figure 1) of probable colonic origin, which was confirmed at endoscopy. An ulcerated, stenosing lesion of the proximal descending colon was biopsied and revealed an extended RAS wild-type adenocarcinoma. Complementary immunohistochemistry showed a microsatellite-stable tumour, hence exclusion of Lynch syndrome was not sought. She was referred to our multidisciplinary team meeting, where liver disease was deemed unresectable by an experienced hepatobiliary surgical team and was proposed for upfront palliative chemotherapy.

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Figure 1 CT scan at baseline, showing large-volume hepatomegaly with extensive infiltration due to unresectable liver metastases.

At her first medical oncology consult, she was medically fit (Eastern Cooperative Oncology Group performance status 1) and became asymptomatic with prescription of opioids. On physical examination, she was pale, anicteric and had a palpable liver 20 cm below her rib cage. No other alterations were found in her cardiopulmonary or neurological examinations. Laboratory tests revealed mild anaemia of 101 g/L (normal range: 120–160 g/L) and leucocytosis $14.5 \times 10^9/L$ ($1.8\text{--}8.0 \times 10^9/L$), normal baseline creatinine with a Cockcroft-Gault estimated creatinine clearance (ClCr) of 2.25 mL/s/m² ($1.24\text{--}2.00$ mL/s/m²) and Child-Pugh class A liver dysfunction with total bilirubin twice the upper limit of normal (ULN), normal albumin and normal international normalised ratio, moderate cytolysis with aspartate aminotransferase 9 times the ULN, alanine aminotransferase 3 times the ULN, as well as severe cholestasis with gamma-glutamyl transferase 22 times the ULN and alkaline phosphatase 3.5 times the ULN. Initial LDH level was 55.51 $\mu\text{kat/L}$ ($2.09\text{--}3.67$ $\mu\text{kat/L}$). Treatment options were discussed with the patient, and considering her high-volume hepatic disease and liver dysfunction, she gave written consent to first-line chemotherapy with FOLFOX-6 and addition of monoclonal antibody cetuximab further on, as clinically tolerated.

She started full-dose chemotherapy, composed of oxaliplatin (85 mg/m²), 5-fluorouracil bolus and 46 hours continuous infusion ($400\text{ mg/m}^2 + 2400\text{ mg/m}^2$) every 15 days through a central venous catheter. She was prescribed corresponding antiemetic prophylaxis and supportive therapy. Mild nausea after the first cycle was promptly mitigated with ondansetron. Close analytical monitoring revealed descent of total serum bilirubin levels to normal, lowering of transaminases to mild cytolysis with stable cholestasis levels.

After completing three cycles of chemotherapy, she presented to our outpatient clinic with *de novo* mild asthenia and subjective fidgetiness with observable fine tremors of her hands.

INVESTIGATIONS

Blood work-up showed serum creatinine of 124 $\mu\text{mol/L}$ ($53\text{--}97$ $\mu\text{mol/L}$) with ClCr of 1.29 mL/s/m² and hyperkalaemia of 6.7 mmol/L ($3.5\text{--}5.1$ mmol/L). ECG showed no abnormalities. Intravenous fluids and potassium-lowering measures were

initiated, but she maintained her complaints. Four hours later, laboratorial reevaluation revealed creatinine of 115 $\mu\text{mol/L}$, potassium levels of 5.9 mmol/L, high serum phosphate—1.71 mmol/L ($0.74\text{--}1.52$ mmol/L)—and low ionised calcium—1.14 mmol/L ($1.16\text{--}1.34$ mmol/L). Uric acid levels were also high—803 $\mu\text{mol/L}$ ($155\text{--}357$ $\mu\text{mol/L}$).

TREATMENT

Clinical TLS was diagnosed and she was admitted to the intensive care unit (ICU) for close monitoring, intensive hydration and correction of electrolyte abnormalities. Due to immediate unavailability of rasburicase, no hypouricaemic agent was prescribed. Forty-eight hours after admission, renal function and electrolytes had normalised and uric acid levels were 458 $\mu\text{mol/L}$. At this point, she was prescribed allopurinol at 100 mg per day, with good tolerance. As her analytical parameters continued to improve, with good urine output and normal cardiac monitoring, she was transferred to the general ward for further monitoring and discharged 5 days later.

Shortly after, she referred back to hospital with painful purple lesions on both legs. Physical examination revealed a painful petechial rash up to both knees and hypersensitivity reaction to allopurinol was suspected. Skin biopsy revealed neutrophilic vasculitis. Allopurinol was discontinued and skin lesions regressed. Meanwhile, rasburicase was made available.

After postponing treatment for 1 week, the patient was asymptomatic. Liver was palpable 7 cm below her rib cage with normalised liver function, no cytolysis and mild cholestasis. Since CT scan showed reduction of size of liver metastasis accounting for stable disease according to RECIST V.1.1 criteria, the addition of cetuximab at 500 mg/m² was brought forward. Since there were previous reports of clinical TLS with targeted therapy,^{10 11} secondary prophylaxis for high-risk TLS was considered for this patient. For the following cycles, she was admitted to the ward 2 days prior to chemotherapy administration. She was prescribed intensive fluid therapy with normal saline 2 L/m² daily to achieve an hourly urine output of 100 mL/m², with good tolerance. Four hours before chemotherapy, a single dose of rasburicase was given and she completed three cycles of FOLFOX plus cetuximab with no increase in toxicity. During these hospitalisations, no recurrence of TLS was found.

OUTCOME AND FOLLOW-UP

Re-evaluation CT scan showed reduction of hepatomegaly with smaller liver metastases (figure 2). Low-risk TLS prophylaxis was resumed at our outpatient clinic: a hydration protocol was added to chemotherapy alongside further laboratorial monitoring. Treatment is currently ongoing with good response.

According to the patient, she did not realise how severe her condition was when admitted to the ICU with TLS: she felt her usual self, despite her mild symptoms. And, in spite of the long hydration protocols, she felt safe during subsequent cycles.

DISCUSSION

This case illustrates the challenges of diagnosing and treating TLS in solid tumours.

A systematic literature review in Medline, Embase and Web of Science was performed and showed 17 case reports,^{6 8–23} dating back to 1988. Most were men (11 cases) with median age of 59 years (27–83 years). Seven cases had right-sided and seven had left-sided colon cancer. Molecular profiling was only available in four of them. The liver was the most frequent site of metastatic involvement (14 cases), 4 of them with documented

Figure 2 CT scan after three cycles of FOLFOX and three cycles of FOLFOX plus cetuximab, with regression of liver metastases.

necrosis. Five cases filled criteria for bulky disease. At baseline, eight reported elevation of LDH and seven reported altered renal function. Spontaneous TLS occurred in five cases, while TLS occurred after first-line chemotherapy in six cases. Ten out of 17 patients died due to complications of clinical TLS.

In our case report, hepatic tumour burden was high with concomitant hepatic dysfunction. Concerning TLS in solid tumours, ‘bulky disease’ is defined as: (1) abdominal tumour mass greater than 10 cm, either the primary tumour, retroperitoneal nodes or single liver metastasis or (2) multiple liver metastases with two bigger than 5 cm.¹³ Also ‘extensive metastases’ are defined as producing organ enlargement.²⁴ Known pretreatment risk factors for the development of TLS are high LDH, uric acid, azotaemia and creatinine.⁶ Should these characteristics be present before starting a new treatment, active TLS prophylaxis must be considered. While there have been attempts to quantify colon-specific tumour burden,²⁵ these have not yet been externally validated and their TLS predictability is unknown.

Choice of chemotherapy regimen and dose was key for this patient’s good clinical response. Further addition of cetuximab, directed to RAS wild-type colon cancer, is expected to further decrease tumour size. While chemosensitivity in colon cancer is low, tumour burden and extent seem to be better at predicting TLS, as reported by other authors.²⁴

In the setting of AKI developing during chemotherapy, the differential diagnosis should entail common causes such as dehydration, hypotension, exposure to nephrotoxic drugs and obstructive uropathy, as well as TLS. When the latter case is suspected, prompt laboratorial confirmation of diagnosis and urgent treatment should be sought. Admission to an ICU for continuous cardiac monitoring and laboratorial reevaluation every 4–6 hours is advisable.²⁶ The main aim is to prevent severe cardiac events (arrhythmias or cardiac arrest) and to reverse crystal nephropathy. When the latter is not possible, adequate renal replacement therapy (RRT) may be life saving. Irrespective of the methods used, indications for RRT are the same as for AKI of other aetiologies: low urine output, fluid overload, intractable hyperkalaemia, persistent hyperphosphataemia and symptomatic hypocalcaemia.^{1 26 27} However, lower thresholds should

be used for RRT initiation, since rapid electrolyte changes may develop during TLS.

Rasburicase should be readily available for treating TLS. This genetically engineered enzyme (urate oxidase) is the only compound able to degrade urate crystals and revert nephropathy, thus decreasing the need for RRT. Recommended dosing is 0.2 mg/kg once daily up to 7 days. However, one single dose may lower uric acid levels effectively. It is contraindicated in people with known glucose-6-phosphate dehydrogenase deficiency due to development of severe haemolysis and fatal methaemoglobinaemia.²⁸

In such cases or if otherwise unavailable, allopurinol might be used alternatively. It reduces the formation of new urate crystals. Dose should be reduced to 50% in the setting of AKI and is, therefore, precluded in acute clinical TLS. Recommended dose in adults is 100 mg/m² every 8 hours up to 800 mg daily. The occurrence of a hypersensitivity-related skin toxicity in this patient limited the use of allopurinol. Although severe forms of this cutaneous reaction have been associated with HLA-B*58:01 polymorphisms in Asian populations,²⁹ screening of such allele is not advised in other populations.

There is limited evidence for the feasibility of secondary prophylaxis of TLS in the literature. Since adding targeted therapy would further increase this patient’s risk of TLS, high-risk prophylaxis was required. Rasburicase at a single dose of 0.2 mg/kg is well tolerated and prevents morbidity and mortality in such patients.⁵ After confirming decrease of disease burden at radiological assessment, low-risk prophylaxis was prescribed with no recurrence of TLS. However, in the event of disease progression, TLS prophylaxis with rasburicase and hydration is advisable subsequent lines of treatment.

In conclusion, although the patient presented with risk factors for TLS, high-risk prophylaxis was not considered. Yet, prompt diagnosis, treatment and secondary prophylaxis enabled good response to chemotherapy.

Learning points

- ▶ Tumour lysis syndrome (TLS) is a rare oncological emergency in solid tumours. However, physicians should be aware that high tumour burden, high proliferation rates and chemosensitive tumours are at increased risk of TLS.
- ▶ Differential diagnosis of acute kidney injury (AKI) occurring during chemotherapy should include TLS. Prompt diagnosis is crucial for short-term outcome.
- ▶ Once diagnosed, TLS warrants admission to intensive care unit for close monitoring, management of electrolyte imbalances and prevention of AKI, eventually with use of renal replacement techniques.
- ▶ Use of uricolytic drugs such as rasburicase (preferable) or allopurinol are not exempt of toxicity, which should be considered on prescription.

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