

Case Report: Acute Tumour Lysis Syndrome

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Abstract

Introduction: Acute tumour lysis syndrome (ATLS) is a potentially lethal but preventable complication of oncological treatment. **Clinical Picture:** We report a case of a patient with Burkitt's leukaemia who developed ATLS after treatment with chemotherapy. **Treatment:** Standard preventive measures using aggressive hydration, urine alkalinisation and uricosuric agents were instituted before chemotherapy. **Outcome:** However in spite of adequate measures, the patient succumbed to the sequelae of ATLS. **Conclusions:** It is therefore important to identify patients who are at a high risk of developing ATLS so that additional measures can be taken to prevent it from occurring.

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Introduction

Acute tumour lysis syndrome (ATLS) is one of the most urgent of all oncological treatment-related complications. It has a broad impact on organ dysfunction, the most important and life threatening complication being acute renal failure. Early implementation of preventive measures can have a drastic impact on reducing the associated morbidity and mortality from this syndrome. ATLS comprises the following metabolic abnormalities:

- 1) hyperuricaemia,
- 2) hyperphosphataemia,
- 3) hypocalcaemia,
- 4) hyperkalaemia, and
- 5) azotemia.

It commonly occurs after the treatment of rapidly dividing myeloproliferative and lymphoproliferative disorders such as Burkitt's lymphoma and acute lymphocytic leukaemia (ALL). It has also been reported following the treatment of chronic lymphoid leukaemia, breast carcinoma and small cell carcinoma.¹⁻³ Although ATLS may occur spontaneously in these patients, it is particularly liable to occur following treatment with corticosteroids,⁴ post surgery or radiotherapy. The nature and severity of the metabolic abnormalities are variable, depending on:

- 1) tumour burden and its consequent magnitude of intracellular ion and solute release, including urate precursors, phosphates and potassium;
- 2) timing and intensity of chemotherapy;

- 3) underlying renal function, and
- 4) preventive measures instituted.

Case Report

A 68-year-old Chinese man was admitted on 27 February 1999 for fever, lethargy and cough of one week's duration and bilateral ptosis. Significant physical findings on admission were bilateral cervical and right axillary lymphadenopathy, hepatomegaly, bilateral ptosis and complete ophthalmoplegia. He was afebrile on admission and fully orientated.

Initial investigations revealed a haemoglobin of 13.7 g/dL, white cell count of $17.7 \times 10^9/L$ and platelet count of $57 \times 10^9/L$. The prothrombin time and partial thromboplastin time were normal at 12.0 and 24.5 seconds, respectively. Apart from a raised serum uric acid level of 699 $\mu\text{mol/L}$ (normal range 232 to 494), his serum biochemistries were all normal (Table I).

Bone marrow aspirate was consistent with ALL L3 (Burkitt's leukaemia). Cytogenetic studies revealed multiple clonal abnormalities including $t(8;22)(q24;q11)$. Magnetic resonance imaging (MRI) of the brain revealed partial thrombosis in both cavernous sinuses and lumbar puncture showed leukaemic cells present in the cerebrospinal fluid. In addition, the chest X-ray showed widespread bilateral lung infiltrates.

He was commenced on oral allopurinol, aggressively hydrated with intravenous fluids and alkalinised with 8.4%

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TABLE I: TREND OF SERUM BIOCHEMISTRIES PRE- AND POST-CHEMOTHERAPY

	27 February 1999	28 February 1999	1 March 1999	4 March 1999 (12 hours post- chemotherapy)
Urea (mmol/L)	2.8	4.5	9.2	16.6
Creatinine (umol/L)	69	72	77	167
Sodium (mmol/L)	132	134	139	148
Potassium (mmol/L)	4.7	3.8	3.5	5.8
Bicarbonate (mmol/L)	15.6	18.4	18.3	4.4
Calcium (mmol/L)	2.46	.	.	2.29
Phosphate (mmol/L)	0.80	.	.	5.34
Uric acid (umol/L)	699	620	751	451
LDH (u/L)	.	4468	.	17905
Arterial pH	.	7.410	.	6.651

LDH: lactate dehydrogenase

sodium bicarbonate to maintain a urine pH of above 7.0. Intravenous ceftazadime and oral erythromycin were started for pneumonia. Intravenous corticosteroids were initiated for the therapy of his leukaemia on the day of admission. On the fourth day of admission, further chemotherapy with intravenous vincristine 2 mg and cyclophosphamide 800 mg was given. His serum uric acid was 751 $\mu\text{mol/L}$ and creatinine 77 $\mu\text{mol/L}$.

Twelve hours following chemotherapy with vincristine and cyclophosphamide, he became severely breathless and agitated. Arterial blood gases revealed severe acidosis with a pH of 6.651, standard bicarbonate of 2.2 mmol/L with a base excess of -30.9 , pO_2 of 92.2 mmol/L and pCO_2 of 34.0 mmol/L (on 40% oxygen). His urea was 16.6 mmol/L, creatinine 167 $\mu\text{mol/L}$, potassium 5.8 mmol/L, lactate dehydrogenase (LDH) 17905 u/L, corrected calcium 2.71 mmol/L and phosphate 5.34 mmol/L (the calcium/phosphate product was 14.5). He collapsed shortly after and failed to respond to maximal resuscitative measures.

Discussion

Risk Factors for the Development of ATLS

With current standard preventive measures, the risk of developing ATLS is low. However, it is important to identify highly predisposed patients. High-risk factors include patients with pretreatment renal insufficiency (serum creatinine $>132 \mu\text{mol/L}$). The development of azotemia also correlates with high pretreatment serum LDH levels.⁵ A risk factor scoring system was proposed using the following parameters: disease bulk, marked sensitivity to the treatment modality, preceding renal impairment, high serum LDH and uric acid⁶ (Table II).

Prevention and Treatment of ATLS

Adequate hydration is very important in the prevention and treatment of ATLS. Urine output and central venous

TABLE II: RISK SCORE FOR ASSESSING THE LIKELIHOOD OF DEVELOPING ATLS⁶

Parameter	Score
Bulky disease	2
Marked sensitivity to treatment modality	2
Renal impairment	1
Raised serum LDH	1
Raised serum uric acid	1

ATLS: acute tumour lysis syndrome; LDH: lactate dehydrogenase

Score: 4-7 = high risk; 3 = medium risk; <3 = low risk

pressure should be monitored closely. The urine pH should be kept above 7.0 through the use of sodium bicarbonate. Overzealous alkalization should be avoided as this may cause precipitation of calcium phosphate and aggravation of hypocalcaemic symptoms. Forced diuresis, using loop diuretics, maintains adequate urinary flow and has a phosphaturic action. However, it should be avoided in the face of hypovolaemia as it may contribute to intratubular precipitation of uric acid and calcium phosphate in the volume depleted patient.

Haemodialysis should be considered in the following situations:

- 1) persistent hyperkalaemia despite conventional treatment,
- 2) fluid overload and poor urine output ($<125 \text{ mL/m}^2/\text{h}$),
- 3) rapidly rising phosphate levels despite intervention or inability to maintain a high urine flow rate in the face of hyperphosphataemia,
- 4) symptomatic hypocalcaemia despite treatment, or
- 5) hyperuricaemia.

The administration of allopurinol, a potent inhibitor of xanthine oxidase is also important for the prevention or treatment of hyperuricaemia. Uricozyme (a non-recombinant urate oxidase) may also be used in place of allopurinol. Urate oxidase (uricase, uricozyme) is a proteolytic enzyme extracted from *Aspergillus flavus*. It degrades uric acid to allantoin, which is 5 to 10 times more soluble than uric acid and is readily eliminated by the kidneys (Fig. 1). However, it is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because it induces haemolysis secondary to its oxidant effect. The advantages of urate oxidase over allopurinol are:

- 1) oral administration may not be feasible in patients with severe emesis or mucositis,
- 2) absence of xanthinuria which may contribute to renal impairment,
- 3) rapid decline of uric acid,
- 4) absence of drug interactions with certain chemotherapeutic agents, for example mercaptopurine and azathioprine.

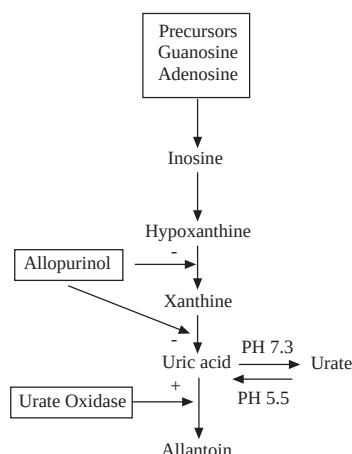


Fig. 1. Metabolic pathway of uric acid

In a trial where uricozyme was administered to 134 children with ALL or advanced non-Hodgkin's lymphoma, patients given urate oxidase had rapid and significantly greater decreases in serum uric acid levels and lower serum creatinine and urea levels compared with 129 similarly treated historical controls who had received allopurinol.⁷

Summary

ATLS is a potentially preventable syndrome. Although the incidence is low with standard preventive measures, the effects can be fatal or associated with significant morbidity. The argument for giving less or more gentle chemotherapy upfront remains controversial as this may compromise the chances of treatment success in these patients. Therefore patients at high risk of developing this syndrome should be identified and the following additional measures instituted:

- 1) hyperhydration with 3 L/m²/day,
- 2) allopurinol 600 mg daily for the first 2 days of chemotherapy followed by the standard 300 mg daily,

- 3) the use of urate oxidase instead of allopurinol especially in renal impairment,
- 4) daily monitoring of tumour lysis markers and renal function, and
- 5) the measurement of central venous pressure, preferably in an intensive care setting.

Our patient had a score of 6 and was at a high risk of developing ATLS at diagnosis. Preventive measures were taken upon admission in an attempt to decrease morbidity and mortality from ATLS. Even his chemotherapy was attenuated. However, as he had very aggressive disease, he required treatment urgently for his leukaemia. The only measure that could have possibly improved management was the insertion of a central venous catheter and monitoring this patient in the intensive care unit.

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