# Case Study

## Tumour Lysis Syndrome in a Neonate with Transient Abnormal Myelopoiesis

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**ABSTRACT**

**Background**
Tumour lysis syndrome (TLS) is an oncological emergency associated with haematological malignancies or highly proliferative solid tumours, commonly after chemotherapy. It is rarely associated with transient abnormal myelopoiesis.

**Observation**
We report a rare case of a neonate with transient abnormal myelopoiesis and tumour lysis syndrome, complicated with concomitant heart failure due to an underlying atrioventricular septal defect. Hyperhydration was contraindicated due to heart failure. The patient was managed conservatively with full recovery.

**Conclusion**
Tumour lysis syndrome should be suspected in neonates with transient abnormal myelopoiesis with electrolyte abnormalities. Treatment options should be considered carefully for their risks and benefits.

## INTRODUCTION

Tumour lysis syndrome (TLS) is an oncological emergency characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia due to rapid destruction of tumour cells.[1] It may be defined clinically or by laboratory investigations.[2] Cairo and Bishop proposed a laboratory definition which requires two or more abnormal values of uric acid, potassium, phosphorus, and calcium within three days before or seven days after cytotoxic therapy.[2]

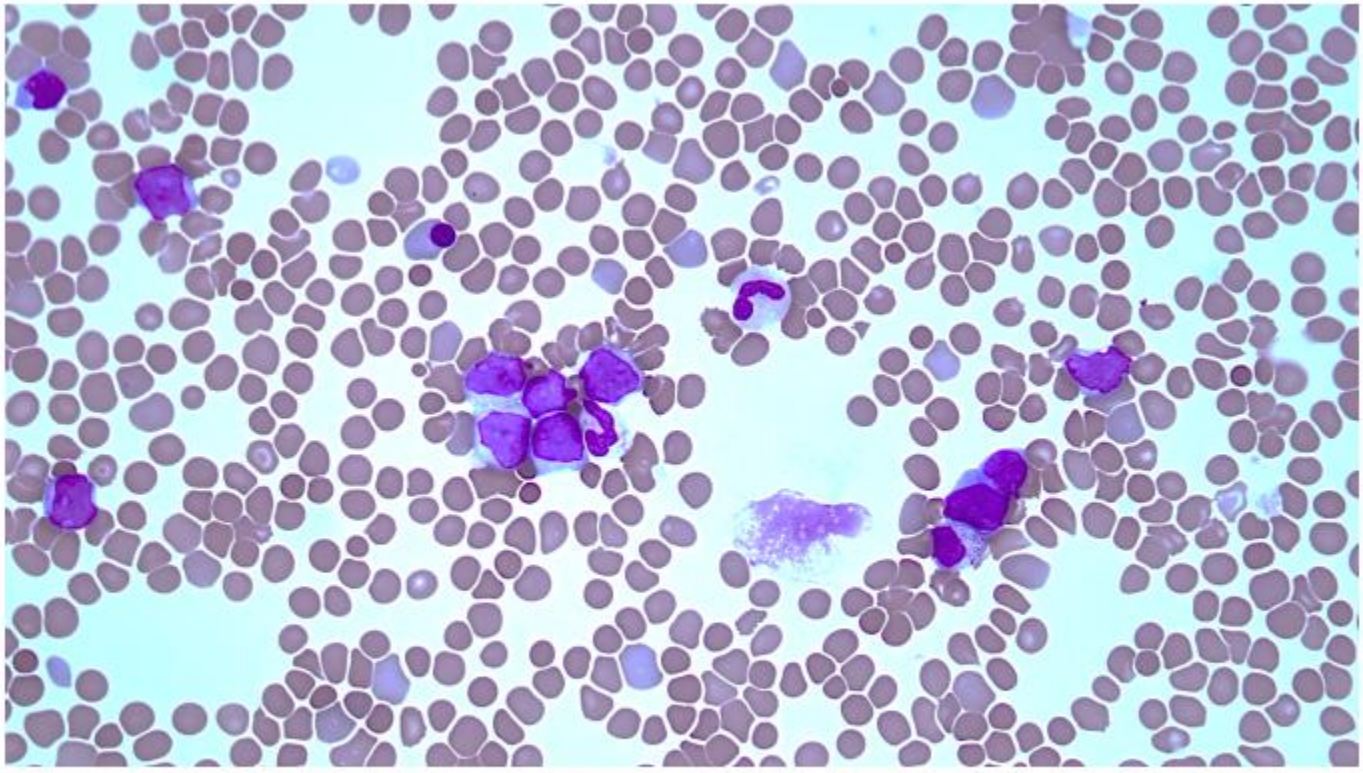
Meanwhile, clinical TLS is defined as laboratory TLS plus at least one clinical complication that was not directly or probably attributable to a therapeutic agent, namely increased serum creatinine concentration (≥1.5 times the upper limit of normal), cardiac arrhythmia/sudden death, or a seizure.[2] These are the most used definitions of TLS, although no universal consensus has been reached.[1]

TLS is generally associated with haematological malignancies or high proliferative and sensitive solid tumours.[3] It rarely occurs in transient abnormal myelopoiesis (TAM).[4] TAM is a disorder of foetal haematopoiesis occurring mostly in neonates with Down Syndrome.[4] We report a case of a patient with TAM who developed tumour lysis syndrome.

**Case Report/Case Presentation**

A baby girl was born prematurely at 34 weeks by spontaneous vertex delivery with a birth weight of 2390g. Her mother is a healthy 28-year-old lady. Detailed scan performed at 24 weeks showed a ventricular septal defect with hyperechogenic bowel. Thus, amniocentesis was performed and revealed Trisomy 21.

The patient was admitted to the neonatal intensive care unit (NICU) after delivery. She exhibited clinical features of Down Syndrome, namely single palmar crease, wide sandal gap, hypotonia and loose skin folds at posterior neck. Initially she was saturating well under room air however, at 12 hours of life she started to develop respiratory distress requiring supplemental oxygen. An ejection systolic murmur grade 3/6 was heard on chest auscultation. Echocardiography revealed complete balanced atrioventricular septal defect with moderate bilateral branch pulmonary artery stenosis. The baby eventually exhibited signs of heart failure, namely persistent tachypnoea with a displaced apex beat.



Picture 1: Full blood picture showing leucoerythroblastic picture with presence of large blasts with high nuclear:cytoplasmic ratio and multiple prominent nucleoli.

Pharmacological treatment was commenced on day 6 of life, with initiation of oral Furosemide 1 mg/kg/dose twice a day, and oral Spironolactone 3.125mg BD. Subsequently, Captopril was added as a third anti-failure medication a fortnight later and doses were gradually increased to maximum therapeutic dose.

Initial laboratory reports on the day of birth revealed haemoglobin of 17.8g/dL, total white count of $65x10^3$/uL and platelet count of 93 $x10^3$/uL. A full blood picture (FBP) performed at 48 hours of life

suggested Transient Abnormal Myelopoiesis (TAM) with a blast percentage of 42% as shown in Figure 1. There was no coagulopathy at this time.

Other blood investigations taken at day 4 of life showed hypocalcemia and hyperphosphatemia with normal potassium and serum uric acid levels. Here, two out of four criteria for laboratory TLS were fulfilled. Hyperkalemia and hyperuricemia became evident at day 7 and day 9 of life respectively and remained elevated on repeated readings. Her serum creatinine on day 9 of life was 62 μmol/L which was more than 1.5 times from the upper limit of normal. It was at this stage that criteria for both laboratory and clinical TLS were fulfilled. Table 1 shows results of her serial blood investigations throughout admission.

Management of the child was mainly supportive. Hyperhydration was not commenced due to concomitant heart failure. Total fluid infusion was kept at 140 ml/kg/day. Serum electrolytes normalized after resolution of leukocytosis on day 16 of life. During this period, highest ventilatory support was non-invasive ventilation. Opinion from the paediatric haematology team was sought, who advised against allopurinol or rasburicase. Serial peripheral blood examination showed complete resolution in the number of circulating blasts by day 79 of life.

The patient's heart failure worsened, and she was put on the waiting list for surgical correction. However, at 2 months old, she developed an acute life-threatening event requiring cardiopulmonary resuscitation and prolonged ventilatory support. This resulted in a multidisciplinary team decision for palliative care. She was eventually discharged at 3 months with three anti-failures.

## DISCUSSION/CONCLUSION

We report a case of a neonate who developed spontaneous tumour lysis syndrome associated with transient abnormal myelopoiesis, complicated by concomitant heart failure.

Transient Abnormal Myelopoiesis is considered a pre-leukaemic disorder occurring mainly in infants of Down Syndrome. The occurrence of trisomy 21 with an additional single GATA1 mutation, drives foetal liver haematopoiesis leading to proliferation of megakaryoblastic progenitor cells[5,6]. The transient nature is thought to be due to the switching of foetal liver to bone marrow at the site of haematopoiesis as the infant matures.[6] However 10-20% of these patients will develop Acute Megakaryoblastic Leukaemia.[5]

Leukocytosis and presence of blast cells more than 10% on a peripheral blood smear suggest the diagnosis of TAM.[7] Thrombocytopenia may be present in 40% of cases.[8] Diagnosis is confirmed by spontaneous regression of blast cells on peripheral blood film within weeks to months.[9] Neonates with TAM may have hepatomegaly, splenomegaly, jaundice, bleeding tendencies, ascites, pleural effusion, and renal failure.[9] They are usually managed conservatively. In patients with evidence of end-organ dysfunction, exchange transfusion, chemotherapy and leukapheresis may be carried out.[10]

The mainstay management of tumour lysis syndrome is also supportive. Allopurinol, rasburicase and loop diuretics have been suggested as potential pharmacological therapy. The patient gradually recovered after treatment with diuretics and a small increment in fluid volume.

While most cases resolve spontaneously, there are several risk factors that warrant therapeutic interventions, including signs of hyper viscosity, extremely high blast count, respiratory compromise due to hepatosplenomegaly or heart failure not due to congenital heart disease, and disseminated intravascular coagulation.[11] The risk of TLS is higher in patients with high tumour burden, rapidly proliferating cells, sensitivities to chemotherapy agents or those with underlying renal impairment, and mortality is associated with organ failure.[12] In our case, prematurity and hyperleukocytosis were significant factors that stratified her into the high-risk category. Interestingly, a high blast percentage count at time of presentation is not a determinant for therapeutic interventions or a risk factor to predict early death in these infants.[12]

In addition, this patient had a higher physiological and haemodynamic demands on her kidneys, due to prematurity and concomitant heart failure. The immature cells i.e., blasts in transient abnormal myelopoiesis are easily ruptured. Consequently, this will lead to massive spillage of intracellular contents such as potassium, phosphate and nucleic acid into the extracellular space resulting in hyperkalemia, hyperphosphatemia and hyperuricemia due to increased catabolism of nucleic acid into uric acid. These electrolytes are renally excreted and their capacity to compensate for these changes is markedly reduced in this patient. Therefore, excess uric acid will form stones causing obstructive uropathy and subsequently progress into acute kidney injury.

To our knowledge, only four cases of tumour lysis syndrome in association with TAM have been reported. Kato et. al.[13] reported a case successfully treated with allopurinol and diuretics. Abe et. al.[4] reported a patient who subsequently succumbed despite treatment with diuretics and pressor agents. Tragiannidis et. al.[10] treated a neonate with TLS and TAM with rasburicase and the patient made complete recovery. Singh et. al.[9] described three case reports, one of which was a neonate with Down Syndrome phenotype and atrioventricular septal defect who developed tumour lysis syndrome. The patient succumbed due to obstructive cholangiopathy.

Evidently, while TAM is often self-limiting, it may rarely cause tumour lysis syndrome. Clinicians should have a high index of suspicion of its manifestation with consideration of all treatment options.

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