J R Coll Physicians Edinb 2020; 50: 35–8 | doi: 10.4997/JRCPE.2020.109

A rare cause of tumour lysis syndrome and acute kidney injury

Ala Ali[1], Rawaa D Al-Janabi[2]

Abstract

Tumour lysis syndrome is rare in solid malignancies. Here, we report a case of tumour lysis syndrome and acute kidney injury in a 23-year-old female with gestational trophoblastic neoplasia. Hydration and early dialysis therapy were started with good recovery. On follow up she progressed to chronic kidney disease. After 6 years of follow up, the patient conceived and delivered successfully.

Keywords: acute kidney injury, AKI, gestational trophoblastic neoplasia, GTN, tumour lysis syndrome, TLS

Financial and Competing Interests: No conflict of interests declared

Correspondence to:
Ala Ali
Nephrology and Renal Transplantation Centre
The Medical City
Baghdad
Iraq

Email:
ala.ali@meciq.edu.iq

Introduction

Tumour lysis syndrome (TLS) represents the metabolic derangements resulting after the initiation of chemotherapy for malignant tumours. TLS occurs because of the rapid destruction of tumour cells and the subsequent rapid release of intracellular contents and proteins into the extracellular space. This will lead to hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia and acute kidney injury (AKI).[1]

TLS follows the treatment of haematologic malignancies, such as acute leukaemia and lymphoma. It may also occur after treatment of bulky tumours, especially if highly sensitive to chemotherapy.[2]

There is no uniformly accepted classification of TLS, but the Cairo–Bishop definition is the most commonly used one and includes laboratory and clinical criteria (Table 1). Clinical criteria include renal, cardiac or neurologic dysfunction. These manifestations need to occur within 3–7 days of chemotherapy, and two markers should be abnormal within 24 hours.[3]

Risk–Injury–Failure–Loss–Endstage renal disease (RIFLE) classification or Acute Kidney Injury Network (AKIN) criteria are applied for AKI. These allow for early detection and rapid intervention.[4,5]

Gestational trophoblastic disease represents a range of pregnancy-related disorders, comprising the premalignant disorders of complete and partial hydatidiform mole, and the malignant disorders of invasive mole, choriocarcinoma and the rare placental-site trophoblastic tumour. Invasive mole is a molar pregnancy in which the molar villi grow into the myometrium or its blood vessels. It may extend into the broad ligament and metastasise to the lungs, the vagina or the vulva.[6]

It is very rare to have TLS in a solid tumour, especially in obstetric/gynaecology oncology. Literature review yielded only one case report of TLS in metastatic gestational trophoblastic neoplasia (GTN), reported by Schuman et al.[7] in 2010.

Here, we present a case of TLS and AKI in an Iraqi female with an invasive mole who received aggressive chemotherapy, treated with haemodialysis and followed up for 6 years.

Case presentation

A 23-year-old female with unremarkable history was admitted in 2010 to the obstetrics and gynaecology unit. She was in the fourth month of her first pregnancy. A month previously, she had vaginal bleeding. She sought medical attention and discovered to have GTN, namely an invasive mole. Her β-human chorionic gonadotropin (hCG) level was >100,000 IU/l.

She received two courses of methotrexate and leucovorin 8 days apart with no response. Then the gynaecologist and the oncologist gave four cycles of a protocol comprising bleomycin, etoposide and vinblastine every 5 days. She received two cycles. Prior to the third cycle, she started to pass <1,000 cc/day of urine and her serum creatinine was elevated. The uterine mass was 11 cm in diameter as assessed by ultrasonography (Figure 1) before receiving the first dose of chemotherapy and it had shrunk to 5 cm 5 days after receiving the second cycle of chemotherapy.

On examination, the patient was thin, conscious, pale, ill-looking, mildly dehydrated with deep breathing. She was afebrile with no oedema. Blood pressure was 100/70 mmHg with a regular small pulse at a rate of 110 bpm. Chest examination revealed distinct heart sounds but clear lung

[1]Consultant Nephrologist and Transplant Physician, Nephrology and Renal Transplantation Centre, The Medical City, Baghdad, Iraq; [2]Consultant Gynaecologist and Obstetrician, Baghdad Teaching Hospital, The Medical City, Baghdad, Iraq

Table 1 Cairo–Bishop Classification of tumour lysis syndrome (TLS)[1]

Laboratory TLS		Clinical TLS
Uric acid	>8.0 mg/dl	Acute kidney injury (defined as creatinine >1.5× the upper limit of normal for patient age and sex)
Potassium	>6.0 mEq/dl	Cardiac arrhythmia
Phosphorus	>4.6 mg/dl	Seizure, tetany or other symptomatic hypocalcaemia
Calcium	<7.0 mg/dl	

bases. Table 2 shows the laboratory results at baseline before chemotherapy.

Abdominal ultrasound showed normal size kidneys with no obstruction. Echocardiography revealed mild-to-moderate pericardial effusion with an ejection fraction of 49%.

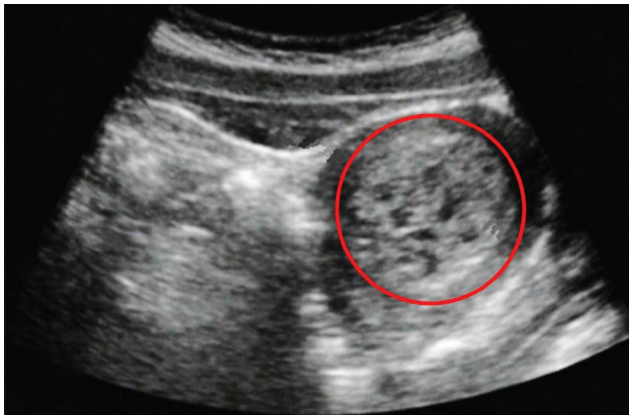
Correction of her hydration status was carried out by infusing 2 l of isotonic normal saline, as well as antihyperkalaemic measures. Allopurinol was administered in a dose of 300 mg/day. Rasburicase was not available in the hospital. A right internal jugular vein dual lumen catheter was inserted, and the patient received daily haemodialysis for 6 days. She developed one episode of supraventricular tachycardia, not on dialysis, which was controlled medically. At day 7, she was haemodynamically stable, and urine output was approximately 2,000 cc/24 hours.

Table 2 shows renal indices and electrolytes before dialysis and 1 week after dialysis.

At day 14, the patient's creatinine was 1.3 mg/dl and the haemodialysis catheter was removed. One month later, she received gentle chemotherapy with a single course of etoposide at 50% of the original dose. Serum creatinine was 1.29 mg/dl with unremarkable urine exam. At the end of the third month, the uterus was clear, β-hCG was undetectable and the serum creatinine level was 1.29 mg/dl. She was scheduled for follow up every 3 months.

After 6 months, the patient was asymptomatic but with a creatinine of 1.5 mg/dl, serum potassium of 5.7 mEq/l and uric acid of 4.1 mg/dl. Urine examination revealed leukocyte casts and urate crystals. There were no excess eosinophils in blood nor in the urine. Arterial blood gas analysis was normal. Ultrasound showed echogenic kidneys; the size of the right one was 9.4 x 3.7 cm while the left was 9.4 x 4.8 cm and a parenchymal thickness of 16 mm. The patient denied using any drugs, even simple analgesics. After discussion with the patient, her family and the treating gynaecologist, renal biopsy was performed under real-time ultrasound guidance. Renal histopathology was consistent with a chronic tubulointerstitial disease (Figure 2).

Figure 1 Abdominal ultrasound with 11 × 10 cm invasive mole (circle)



The patient continued follow-up visits for the next 18 months. Her blood pressure was maintained at approximately 120/85 mmHg and serum creatinine plateaued at 1.5 mg/dl. Months later her blood pressure started to escalate to 170/100 mmHg, and creatinine was 1.7 mg/dl. She had 1.1 gm urinary protein over 24 hours. Serum K and haemoglobin levels were within normal range. Renal size was the same as the previous visit. Blood pressure was controlled by diltiazem 90 mg/day and ramipril 5 mg/day. Renal function and urinary protein excretion of <1 g/24 hour were stable for approximately 2 years.

At the end of 2016, 6 years after her initial insult, the patient presented for help with conception. She was clinically asymptomatic with well-controlled blood pressure. Her creatinine was 2.2 mg/dl (estimate of actual glomerular filtration rate of 29 ml/min/m^2 by body surface area) and a urine protein excretion of 1 g/24 hours. Serum uric acid was 6.1 mg/dl. Renal size was an average of 9 x 4 cm.

After discussion with the family and the obstetrician, the family accepted the risk of becoming pregnant. During pregnancy, blood pressure was controlled with α-methyldopa and labetalol. The maximum creatinine value was 3 mg/dl at 20 weeks of gestation and urinary protein excretion was 2 g/24 hours at 26th week of gestation. Epoetin alfa plus iron and folate were given for anaemia management. She continued maternal care visits until normal vaginal delivery at week 36. Her postpartum course was uneventful, her creatinine is 2.3 mg /dl with controlled blood pressure.

Discussion

TLS is rare in solid tumours. In a literature review from 2014, Mirrakhimov[8] reported 10 cases of TLS in gynaecological malignancies, one of which was associated with GTN. The majority of patients' ages at diagnosis were 47–63 years; however, the patient with GTN was 17 years old, and this is near the same age as our patient, 23 years old. All the patients in Mirrakhimov's review[8] developed TLS within

Table 2 Laboratory results at presentation and after 1 week of treatment

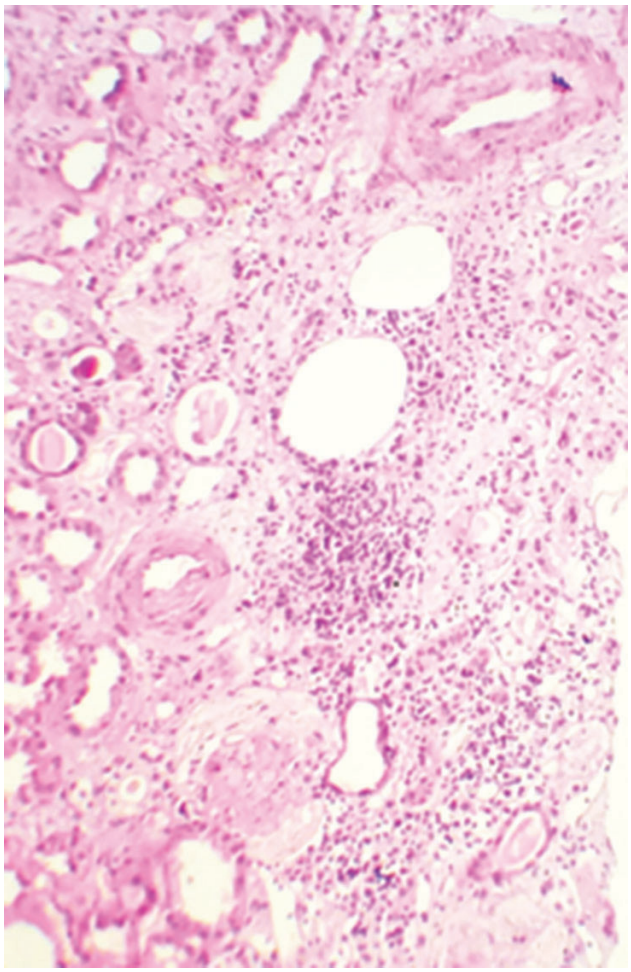
Laboratory test	Baseline (before chemotherapy)	On presentation (pre-dialysis)	1-week later (post-dialysis)
Blood urea	40 mg/dl	200 mg/dl	45 mg/dl
Serum creatinine	1 mg/dl	8.1 mg/dl	1.4 mg/dl
Serum potassium	4.7 mEq/l	6.7 mEq/l	4 mEq/l
Serum calcium	8.3 mg/dl	7.3 mg/dl	8.7 mg/dl
Serum phosphorus	3 mg/dl	7.1 mg/dl	3.8 mg/dl
Serum uric acid	4 mg/dl	15 mg/dl	3 mg/dl
LDH	NA	900 IU	370 IU
pH	NA	7.2	7.41
HCO_3	NA	15 mmol/l	21 mmol/l
Hb%	10.1 g/dl	6.3 g/dl	8.8 g/dl
WBC	4.6×10^9	5×10^9	5×10^9
Platelet count	155×10^9	120×10^9	155×10^9
Urine urate crystals	–	++++	+

+ and ++++ indicate the presence and abundance of urate crystals in the general urine exam.
Hb%, haemoglobin; HCO_3, bicarbonate; LDH, lactate dehydrogenase; NA, not applicable; WBC, white blood cells

2–14 days after starting chemotherapy, our patient developed TLS within approximately 10 days after starting chemotherapy.

Schuman et al.,[7] in their reported case of TLS in metastatic GNT, used methotrexate, leucovorin, etoposide and vinblastine.

Figure 2 Renal biopsy of chronic tubulointerstitial nephritis



In our case, methotrexate and leucovorin were used and TLS developed approximately 10 days after switching onto another regimen principally of etoposide and vinblastine. We think that the development of TLS and AKI in our patient was not only dependent on the type of chemotherapy but also the rapid reduction of the size of the mass. The bulky size responded aggressively to the multiple agents used for the treatment. The initial inadequate hydration state may have augmented the detrimental effect of tumour lysis on the kidneys. In haematological malignancies, awareness of TLS is higher and prophylactic measures are more frequently implemented.[9,10]

In this case, the laboratory and clinical criteria of TLS had been fulfilled with AKI, left ventricular dysfunction and supraventricular tachycardia. AKI results from uric acid crystal deposition in the tubules. Hyperuricaemia may have a role in TLS-associated AKI independent of crystals, possibly by stimulation of inflammation and endothelial dysfunction by a high level of the uric acid rather than by its physical deposition in the renal tubules. Calcium phosphate crystals may also deposit in the myocardium where they may have a role in causing severe arrhythmias.[1,11]

Rasburicase is an undeniably effective and well-tolerated uric acid-lowering agent.[1] In this case, the rapidity of development of AKI and electrolyte disturbances mandated the prompt initiation of dialytic therapy. At the time of presentation, continuous renal replacement therapy was not available. We arranged for a prolonged intermittent daily haemodialysis of 6-hour sessions to reduce the ongoing liberation of different metabolites from the lysing cells. Fortunately, this intervention was successful.

Many studies have linked AKI to chronic kidney disease (CKD) or end-stage renal disease. A US study evaluated the risk of progressive CKD after AKI in patients with a baseline estimate of actual glomerular filtration rate exceeding 45 ml/

min/1.73 m^2. Patients who recovered from AKI with dialysis and then remained dialysis free 30 days after discharge had a 28-fold increased risk of subsequently developing CKD.[12] Failed tubular recovery and subsequent fibrosis would cause the pathologic picture of chronic tubulointerstitial disease as in this report. Hyperuricaemia may contribute to CKD progression, but in this case there was no documented evidence of chronic persistent hyperuricaemia after TLS and AKI recovery.[13]

In a hospital-based study by Prakash et al.,[14] the risk of developing CKD after pregnancy-associated AKI was 4.6%. We did not find long-term data on patients who developed TLS-associated AKI. A literature review by Vodopivec et al.[9] in 2012 described the outcomes of TLS in solid malignancies. There were 58 survivors out of 100 from all the recorded cases between 1983 and 2011.

Pregnancy after chemotherapy-treated choriocarcinoma and an invasive mole is possible as therapy for such is compatible with the preservation of fertility in most women. Full-term and live birth rates of >70% were reported with no risk of congenital abnormalities. The outcome of pregnancy is comparable to the general population but with a slight increased risk of stillbirth.[15,16]

Pregnancy in CKD patients is challenging for both obstetricians and nephrologists. Here, the decision of conception purely depended on the patient's will. Our patient had been counselled and strictly followed during all stages of pregnancy. Fortunately, she did not develop eclampsia and the pregnancy was successful.

Conclusion

TLS should be expected in all chemotherapy-sensitive bulky tumours. Preventive measures should be applied to all patients at risk. Early initiation of renal replacement therapy is the best option in the absence of rasburicase. Maximum care and attention are needed for pregnant women with poor renal function.

Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient/guardian for publication of this paper, including accompanying images.

References

1 Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; 127: 3–11.
2 Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med* 2011; 364: 1844–54.
3 Wilson FP, Berns JS. Onco-nephrology: tumor lysis syndrome. *Clin J Am Soc Nephrol* 2012; 7: 1730–9.
4 Bellomo R, Ronco C, Kellum JA et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204–12.
5 Mehta RI, Kellum JA, Shah SV et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31.
6 Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet* 2010; 376: 717–29.
7 Schuman S, Pearson JM, Lucci JA 3rd et al. Metastatic gestational trophoblastic neoplasia complicated by tumor lysis syndrome, heart failure, and thyrotoxicosis: a case report. *J Reprod Med* 2010; 55: 441–4.
8 Mirrakhimov AE, Ali AM, Khan M. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors* 2014; 6: 5389.
9 Vodopivec DM, Rubio JE, Fornoni A et al. An unusual presentation of tumor lysis syndrome in a patient with advanced gastric adenocarcinoma: case report and literature review. *Case Rep Med* 2012; 2012: 12.
10 Coiffier B. Acute tumor lysis syndrome—a rare complication in the treatment of solid tumors. *Onkologie* 2010; 33: 498–9.
11 Shimada M, Johnson RJ, May WS Jr et al. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. *Nephrol Dial Transplant* 2009; 24: 2960–4.
12 Lo LJ, Go AS, Chertow GM et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int* 2009; 76: 893–9.
13 Li L, Yang C, Zhao Y et al. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. *BMC Nephrol* 2014; 15: 122.
14 Prakash J, Ganiger VC, Prakash S et al. Acute kidney injury in pregnancy with special reference to pregnancy-specific disorders: a hospital-based study (2014–2016). *J Nephrol* 2018; 31: 79–85.
15 Song HZ, Wu PC, Wang YE et al. Pregnancy outcomes after successful chemotherapy for choriocarcinoma and invasive mole: long-term follow-up. *Am J Obstet Gynecol* 1988; 158: 538–45.
16 Gadducci A, Lanfredini N, Cosio S. Reproductive outcomes after hydatiform mole and gestational trophoblastic neoplasia. *Gynecol Endocrinol* 2015; 31: 673–8.