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Pre-treatment tumour lysis syndrome and acute renal failure in adult Nigerians with Burkitt's lymphoma: report of three cases and literature review.

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Summary

Pre-treatment tumour lysis syndrome (pre-TTLS) is not an unusual clinical entity in high-grade lymphomas and lymphoblastic leukaemias. The overall incidence and frequency is unknown and to the best of our knowledge none has been published in Nigeria involving adult females with advanced stage Burkitt's lymphoma (ASBL). Three of the reported cases had pre-TTLS complicated by acute renal failure (ARF). The first two cases had a complete reversal of the ARF with aggressive supportive management and slow introduction of cytotoxic chemotherapy whereas the third case died of ARF due to delay in commencement of aggressive supportive management, chemotherapy and haemodialysis due to financial constraint. This paper stresses the importance of aggressive supportive management and slow introduction of cytotoxic chemotherapy in patients with a stage C and /or stage D Burkitt's lymphoma presenting with pre-TTLS.

Keywords: *Pre–treatment tumour lysis syndrome, acute renal failure, Burkitt's lymphoma.*

Résumé

Le pré-traitment des syndromes d hémolyse des tumeurs (pré-TTLS) n'est pas une entité clinique a haut grade de lymphome et de la leukémie lymphoblastique . L'incidence totale et la fréquence est inconnu et pas documenté aux adulte femeles Nigéria ayant l'étape avancée de lymphome de Burkit. Trois des cas enregistrés avaient le pré-TTLS compliqué avec une chute rénale chronique(ARF). Les deux premiers cas avaient une compléte remission de l'ARF avec des soins intensifs et d'une chémotherapie cytotoxique alors que le 3iéme cas mourut du ARF due au retard des soins intensif,la chémotherapie et l'hémodyalise du au contrainte financiers. Cette étude appuie l'importance des soins de support aggressive et une introduction progressive de la chémotherapie cytotoxique au stage C et D du lymphome de Burkit presentant avec le pré-TTLS.

Introduction

Tumour lysis syndrome (TLS) is a potentially fatal metabolic complication characterized by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia that may lead to acute renal failure (ARF) in patients with rapidly proliferating high-grade lymphomas and leukaemias [1-3]. TLS may occur prior to commencement of cytotoxic chemotherapy. However, it is commonly triggered by chemotherapy, leading to excessive release of large amounts of uric acid and other nephrotoxic agents into the blood stream [4,5]. Risk factors for TLS include large tumour burden (acute leukaemia, high grade lymphomas and bulky solid tumours), high tumour growth fraction and elevated lactate dehydrogenase as well as compromised baseline renal function [6]. Patients with large chemosensitive tumour like endemic Burkitt's lymphoma with a growth fraction of almost 100% and doubling time of about 24 hours are at greatest risk of developing pre-treatment tumour lysis syndrome (Pre-TTLS) [1,2,7]. This could result because of the peculiar cell kinetics and the bulky tumour mass that may outgrow its blood supply, resulting in spontaneous tumour necrosis and concomitant release of intracellular substances into the blood stream. However, by early identification of the pre-chemotherapy risk factors couple with aggressive supportive treatment , ARF is usually reversible. This paper reports and discusses three cases of pre-treatment tumour lysis syndrome (pre-TTLS) in adults with Advanced stage Burkitt's Lymphoma (ASBL) complicated by ARF seen at the University of Maiduguri Teaching Hospital, Nigeria.

Case reports

Case 1

A 20 year old previously healthy young lady presented with two months history of progressive abdominal swelling accompanied by abdominal pain, low grade fever and night sweat and a month history of progressive inability to open the right eye.

At presentation she was chronically ill-looking, anxious but afebrile (Temp. 36.8°C). She was mildly pale (PCV = 28%), anicteric with complete ptosis of the right eye. She weighed 50kg. Her blood pressure was 120/95mmHg and the pulse rate was 108 beats/minute. She was negative for HIV I and II by the Trinity Biotech Capillus rapid screening test kit.

There was no obvious jaw mass. The abdomen was distended by multiple hard craggy masses and she had hepatosplenomegaly of 3cm and 4cm respectively with minimal ascites demonstrable by shifting dullness. The abdominal gait was 78cm at inspiration at the level of the umbilicus. The kidneys were not ballotable. The cardiovascular and respiratory system were unremarkable. Neu-

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rological examination revealed 3rd and 4th cranial nerve palsy with complete ptosis of the right eye.

A provisional diagnosis of a stage D Burkitts lymphoma was made. An abdominal sonography confirmed hepetosplenomegaly with minimal ascites. The para aortic and coeliac lymph node were enlarged, the left kidney was slightly bigger than the right and both ovaries were normal. Aspiration of the abdominal mass revealed very cellular aspirates consisting of diffusely scattered small monotonous round cells with abundant basophilic cytoplasm and cytoplasmic vacuolation. The nuclear chromatin was coarse with multiple small prominent nucleoli characteristic of Burkitt's lymphoma cells. The bone marrow and the cerebrospinal fluid were free from Burkitt's lymphoma cells.

She was commenced on active intravenous hydration with dextrose saline 2.5litres/m^2/day and oral allopurinol 200mg 3x per day for 48 hours while awaiting investigation results. Serum biochemistry showed hyperuricaemia, hyperphosphataemia and hypocalcaemia as well as raised serum urea and creatinine. The potassium was at the upper limit of normal (Table I).

Systemic chemotherapy

* IVCyclophosphamide 1.2g/m^2 spread over 3 days
* IVVincristine 1.4mg/m^2 day 1
* IV Methotrexate 75mg/m^2 spread over 2 days

Treatment continues at 15 days intervals (5 days of active treatment + 9 days of rest, then subsequent therapy starts day 15).

CNS Chemotherapy

- Intrathecal methotrexate 12. 5mg was given on days 1 and 8
- Intrathecal cytosine arabinoside 50mg was given on day 4. CSF was sent for cytology prior to therapy.

On the 5th and 7th day of chemotherapy with active supportive management we noticed a significant gradual improvement in the patients clinical and biochemical results. She had six cycles of systemic and CNS chemotherapy. The right eye ptosis completely disappeared and she was discharged home with normal biochemical result.

Table 1: Biochemistry results of the two cases of pre-TTLS

		At presentation	Day 1 of chemo	Day 5 of chemo	Day 7 of chemo
Case 1	Sodium (135-145mmol/L)	138	136	139	135
	Potassium (3-5mmol/L)	5.0	4.5	3.9	3.4
	Ing. Phosphate (0.6-1.3mmol/L)	1.4	1.3	1.1	0.98
	Bicarbonate (20-30mmol/L)	20	23	21	20
	Uric acid (142-416mmol/L)	1421	989	512	357
	Urea (2.5-5.8mmol/L)	14.2	6.2	4.1	2.8
	Creatinine (44-132mmol/L)	393	184	138	91
	Corrected calcium (2.2-2.7mmol/L)	2.0	2.1	2.34	2.23
Case 2	Sodium (135-145mmol/L)	139	135	138	137
	Potassium (3-5mmol/L)	3.9	4.6	3.4	3.0
	Ing. Phosphate (0.6-1.3mmol/L)	12	1.4	1.1	0.68
	Bicarbonate (20-30mmol/L)	18	17	20	22
	Uric acid (142-416mmol/L)	986	988	520	328
	Urea (2.5-5.8mmol/L)	9.4	10.5	6.9	3.7
	Creatinine (44-132mmol/L)	248	417	268	124
	Corrected calcium (2.2-2.7mmol/L)	2.0	1.8	2.1	2.26

The urinalysis was unremarkable apart from proteinuria of 1+, specific gravity of 1.025 and P^H of 5.0. She was able to make about 100mls of urine per hour throughout the 48 hours of supportive management. Other haematological parameters are within normal limit and adequate for the commencement of chemotherapy.

Definitive systemic and central nervous system (CNS) chemotherapy was commenced after 48 hours as follows:

Case 2

A 17 year old young lady was referred from the State Specialists Hospital Maiduguri with a working diagnosis of ? abdominal tuberculosis. She was initially seen by a medical officer and gave a three months history of abdominal and leg swelling and a five months history of progressive weight loss.

Physical examination revealed chronically ill-looking lady, pale (pcv = 30%) and afebrile (Temp. 37.1°c). She

weighed 48.7 kg. Her blood pressure was 112/95mmHg and the pulse rate was 78 beats per minute. The abdomen was distended by firm, irregular masses and she had hepatosplenomegaly of 6cm and 5cm respectively with distended superficial abdominal veins above the umbilicus, which drained upwards. The abdominal gait was 80cm and ascites was demonstrable by fluid thrill. The kidneys were not ballotable. Other systems were unremarkable.

Abdominal ultrasonography confirmed hepatosplenomegaly with ascites, slightly enlarged kidneys and involvement of the left ovary as well as enlargement of the mesenteric lymph nodes.

Three separate aspiration of the abdominal masses all confirmed Burkitt's lymphoma at least a stage C [9] disease. The marrow and the cerebrospinal fluid were free from burkitt's lymphoma cells. ESR was 65mm/hr, mantoux test and HIV screening were both negative.

She was immediately commenced on active hydration with dextrose saline 2.5 litres/m^2/day and oral allopurinol 200mg 3x per day for 48 hours while awaiting investigation results. Initial serum biochemistry showed metabolic acidosis, hyperuricaemia and hypocalcaemia as well as raised serum urea and creatinine (Table I). Urinalysis revealed urine specific gravity of 1.012 and p^H of 5.0. Repeat serum biochemistry before commencement of chemotherapy showed evidence of Pre-treatment TLS and ARF (Table 1). Haematological parameters are within normal range and adequate for commencement of chemotherapy.

Active rehydration with dextrose saline was increased to 3 litres/m^2/24 hours and she was placed on 50mmol/L of 8.4% sodium bicarbonate to run 6 hourly for 24 hours to keep the urine alkaline (p^H>7.0). At the same time systemic chemotherapy was slowly introduced as outlined in the first case. On the 5th day of definitive and active supportive management, the patients clinical and biochemical parameters started improving. She had six cycles of systemic chemotherapy and 3 cycles of CNS prophylaxis. She was discharged home in good clinical and haematological remission.

Discussion

Tumour lysis syndrome is preventable. Regrettably, however, it results in death for some patients. The first and the second patients had laboratory pre-TTLS whereas the third case had clinical pre-TTLS. Kedar and colleagues at the University of Florida tried to distinguish between Clinical and Laboratory TLS in a retrospective chart review of 30 patients with acute lymphoblastic leukaemia or acute myeloblastic leukaemia treated at their institution. They found that 21 of 30 patients studied had laboratory TLS and only 1 had Clinical TLS [8]. Patients were considered to have laboratory TLS if they have any 2 of the following within 4 days of chemotherapy; 25% increase in the serum level of phosphate, potassium and uric acid as well as urea nitrogen and 25% decrease in the corrected serum calcium level [9]. Clinical TLS was defined as laboratory TLS plus serum potassium of >6.0mmol/L or acute renal failure. Pre-TTLS can developed as a result of the tumour outgrowing its blood supply, resulting in spontaneous tumour necrosis and release of intracellular components, including potassium, phosphate and nucleic acid. Literature search on pre-TTLS in ASBL was unremarkable because most clinicians and haemato-oncologist routinely give supportive management while awaiting biochemical results that is seldom available for emergencies, and even if available are often obtained too late. This is more so in a developing country like Nigeria where most patients present late and are unable to pay for basic investigation and the cost of chemotherapy. Tumour lysis induced urate nephropathy is a common cause of ARF in patients with ASBL [4,10]. The first two cases had a very high serum uric acid level that probably contributed to the renal failure. However, by early recognition and initiation of supportive management and slow introduction of chemotherapy, ARF was reversed. None of the patients had dialysis. The use of hydration, allopurinol and alkalinization of the urine prior to chemotherapy may prevent the development of TLS. Slow introduction of chemotherapy can reduce the load on the kidneys' capacity for clearance of these intracellular components from killed cells (By spontaneous tumour necrosis or with chemotherapy). The third case had florid features of CNS involvement in addition to the biochemical features of ARF 2^0 to Pre-TTLS at presentation. Therefore CNS complication is a significant contributory and cause of death within a background of ARF in this case. There was also a delay in initiation of active supportive management and haemodialysis due to final constraint.

In view of the scanty literature on the incidence and frequency of pre-TTLS in ASBL patients, clinicians and haemato-oncologists should routinely check the renal function for electrolyte imbalance and initiate early supportive management so as to reduce the mortality from this preventable metabolic complication.

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