Section: Miscellaneous

Case Series

DIAGNOSTIC CHALLENGES FACED BY A STANDALONE REFERENCE LAB OF EASTERN INDIA IN DETECTING TLS IN EARLY ONSET PROSTATE CANCER: A VERY RARE CASE SERIES

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ABSTRACT

Background: Tumor lysis syndrome (TLS) is a critical medical condition which arises from the rapid breakdown of tumor cells, leading to significant metabolic disturbances like hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia. These disturbances can result in severe complications, even death. TLS is most common in hematological malignancies with an incidence as high as 42%. However in solid tumor, its prevalence is only 10% with high mortality rate (about 45%). Thus, timely diagnosis and treatment initiation are of paramount importance. In cases of solid tumors, patients who present with laboratory TLS (LTLS) have the median age of presentation of 58 years. Also, the most common solid tumors prone to developing TLS are hepatocellular carcinomas, lung cancer, melanoma, breast cancer followed by prostate and colon cancers. So the presentation of TLS in prostate cancer in young patients of age 40 and 37 years is unique in our case report. TLS has no specific biomarker and point of care testing (POCT) for diagnosis, thus depends only on correlation of laboratory reports and clinical findings. Here, we describe two cases of 40 year and 37 year old male patients with critically high serum potassium and phosphorus where it was found that the samples had no pre-analytical, analytical and post analytical errors. Through our two cases we have tried to elicit the challenges faced by doctors in standalone laboratories in detecting TLS by only analysing biochemical and hematological parameters in the sample and we have tried to come up with a protocol that may bridge the gap between clinicians and lab medicine professionals. This can be helpful in early correlation, diagnosis and treatment of the patients.

Materials and Methods: 2 cases of early onset prostate cancer patients (40 year old and 37 year old respectively) were considered in this case series. Both had critically high serum potassium and phosphorus values on initial investigation.

Results: After taking complete history of the patients and after ruling out pre-analytical, analytical and post analytical errors in the samples, they were diagnosed with Tumour Lysis Syndrome and were immediately started on treatment. Both patients survived and were doing well on follow-up.

Conclusion: This case series underlines the importance of linking clinical history with lab report and bridging the gap between clinics and diagnostics so that diagnosis of rare but critical cases can be made correctly on time and timely management may be provided to prevent TLS induced mortality.

Keywords: Potassium, Phosphorus, Prostate Cancer, Solid Tumours, Tumour Lysis Syndrome, Standalone laboratory, Docetaxel.

INTRODUCTION

Tumor lysis syndrome (TLS) is a critical medical condition that most frequently occurs in haematological malignancies with rapid cellular turnover rates. This syndrome consists of an array of laboratory findings such as hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia, termed as laboratory TLS, (LTLS) which may be sometimes clinically silent. When clinical complications such as seizures, acute renal failure, and cardiac arrhythmias occur in patients presenting with laboratory TLS, the condition is called clinical TLS (CTLS).

TLS is rare in patients with solid tumors. Its incidence in solid, slowly proliferating neoplasia is ambiguous primarily because solid tumors typically have low cellular proliferation and reduced sensitivity to chemotherapy, which decreases the risk of massive cell lysis and hence limited published case reports. Median age of presentation of TLS in case of solid tumor is 58 years.

Prostate cancer has a late age presentation in males. The majority of new cases have been diagnosed in men aged 65 to 74 (38.2%), with a median age at diagnosis of 66 years.[1] Prostate cancer is rare in men younger than 45, accounting for only 0.5% of all newly diagnosed prostate cancer cases although when present in young male, it can be fast-growing and lethal.

Tumor lysis syndrome (TLS) has no specific biomarker and lack of rapid diagnostic tool exacerbates the clinical challenge for diagnosis. Diagnosis relies primarily on the correlation of history and laboratory report. Acute renal injury is the most common cause of death of TLS in solid tumours.[2] The mortality associated with TLS in patients with solid tumours is higher than that in patients with hematologic cancer. The combination of early onset prostate cancer showing TLS is a very rare medical occurrence,[3] but can be fatal unless timely treatment is provided. Hence for a diagnostic standalone laboratory early procurement of detailed history during sample reception can prove life saving for the patient.

Often there is a disconnect between a standalone laboratory and clinical set up as the samples are sent through various clients to independent laboratory without a clinical history or prescription and sometimes without the important contact number for establishing proper communication as early as possible. Clinicians need quick diagnosis for early management, but for a standalone laboratory, it become challenging to release critical values without proper structured history and clinical correlation as pre -analytical issues involved like wrong vial, haemolysis that is not appreciable to naked eye or non-adherence to temperature protocol during transport can also contribute to abnormal values of electrolytes like potassium and phosphorus that are important parameters for analysing TLS.

Cell lysis due to traumatic puncture, forcefully pushed plunger of syringe, vigorous shaking of vials, improper or lack of centrifugation are some other pre-analytical factors that can also result in pseudohyperkalemia and pseudohyperphosphatemia. Hence ruling out pre-analytical errors and clinically correlating abnormal values of potassium and phosphorus through prompt history taking is important in deciding whether to release the report or repeat the sample for rechecking and then reporting.

Here we describe early onset of prostate cancer in a 40 year old and a 37 year old patient both of whom developed TLS post chemotherapy. In both the cases, we initially only found critically high serum potassium and phosphorus. Thus in this case series, by delineating the steps we undertook to finally arrive at the timely diagnosis of TLS, we have tried to elicit the challenges faced by doctors in standalone laboratories in detecting TLS by only analysing biochemical parameters in the samples. We have come up with a protocol that may bridge the gap between clinicians and lab medicine professionals resulting in early correlation, diagnosis and treatment of the patients.

CASE DESCRIPTION

Patient 1: A sample of a 40 year old male patient was found to have increased serum potassium of value equal to 7.13 mEq/L and phosphorus 8mg/dl, both over critical range [Table 1].

The sample of this case, as depicted in Figure 1, showed that sample quantity was adequate for testing, serum was clear and there was no visible hemolysis, lipemia or icterus. There was no demographic error as Lab ID., patient name, age, gender also matched the details in the vial.

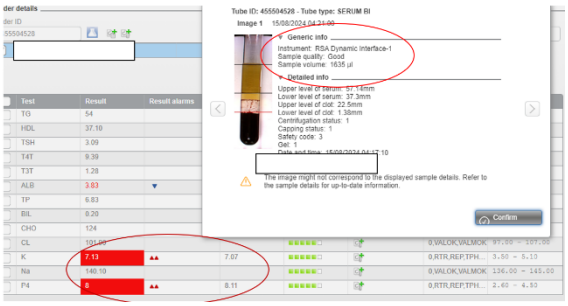

Figure 1: Picture of sample quality and values of parameters taken from middleware. Area of interest to be seen in a sample has already been encircled for reference.

Patient 2:

A sample of a 37 year oldmale patient was found to have increased serum potassium of value equal to 6.17mEq/Land phosphorus 9.72mg/dl both over critical range [Table:2].

As depicted in Figure 2, The sample of this case also showed adequate sample quantity and the serum was clear and there was no visible hemolysis, lipemia or icterus. There was no demographic error too as Lab

ID., patient name, age, gender also matched the details in the vial.

Figure :2 Picture of sample quality and values of parameters taken from middleware. Area of interest to be seen in a sample has already been encircled for reference.

Both the samples were rechecked for serum potassium and phosphate as per recheck criteria (>5.5mEql/L for potassium and >8mg/dl for phosphorus) and there was insignificant difference in result based on bias percentage specific to analytes as per CLIA guidelines [Figure 1], thus ruling out any analytical error. Internal Quality control (IQc) for the analytes had also run thrice in 24 hours as per lab protocol at an interval of 8 hours. 2 levels of IQC were run once at night and 1 level alternately at a gap of 8 hrs each. Our lab follows the IQC protocol of NABL 112A guidelines for a lab working 24 hrs/day for all seven days in week. This guideline follows the ISO 15189: 2022 recommendation for clinical laboratories. On the particular days, before the samples had been processed, QCs that had been run for the parameters had passed. The results were auto transferred through Laboratory Information System (LIS), hence transcriptional error was unlikely. Apart from these parameters, serum uric acid was decreased while total calcium was also slightly low in first patient [Table 1] while in the second patient uric acid was increased and calcium was reduced [Table 2].

Table 1: Summary of Patient 1 relevant results with normal reference range

Parameter	Result	Normal reference range
Phosphorus	8 mg/dl	2.5 – 4.49mg/dl
Calcium	7.5mg/dl	8.5-10.5mg/dl
Uric Acid	2.9mg/dl	3.4-7mg/dl
Potassium	7.13mEq/L	3.5 - 5.1mEq/L
Urea	15.97mg/dl	20-40mg/dl
Creatinine	0.77mg/dl	<1.4mg/dl
TLC	5.8 thou/mm3	4.00 - 10.00 thou/mm3
Hb	11.1g/dl	12.00 - 15.00g/dL
RDW	22%	11.60 - 14.00%
RBC count	3.87mill/mm3	3.80 - 4.80 mill/mm
Mentzer Index	23.6**	

Table 2: Summary of Patient 2 relevant results with normal reference range

Parameter	Result	Normal reference range
Phosphorus	9.72mg/dl	2.5 – 4.49mg/dl
Calcium	6.05mg/dl	8.5-10.5mg/dl
Uric Acid	8.7mg/dl	3.4-7mg/dl
Potassium	6.17 mEq/L	3.5 - 5.1mEq/L
Urea	18mg/dl	20-40mg/dl
Creatinine	1.3mg/dl	<1.4mg/dl
TLC	6.8 thou/mm3	4.00 - 10.00 thou/mm3
Hb	10.3g/dl	12.00 - 15.00g/dL
RDW	16%	11.60 - 14.00%
RBC count	3.96mill/mm3	3.80 - 4.80 mill/mm
Mentzer Index	20.1**	

**Mentzer index is a tool used to differentiate between iron deficiency anaemia and beta thalassemia trait, is calculated by dividing mean corpuscular volume (MCV) by the red blood cell count. If Mentzer Index >13 suggestive of iron deficiency anaemia and < 13 is beta thalassemia trait.

Complete blood count report was found to be otherwise normal except mildly low haemoglobin, with Mentzer index >13 suggestive of iron deficiency anaemia.

As the potassium and phosphorus values were critically high but urea and creatinine values were within acceptable limits indicating no renal derangement affecting the electrolytes hence clinical history of the patient was required before releasing the critically high value. Communication was established with the patients' relatives for clinical history and it was revealed that both patients were known cases of prostate cancer; patient 1 for past 6 months (Stage IIIB Gleeson Score 8) and patient 2 for past 3 months (Stage IIIB Gleeson Score 7) with both showing involvement of seminal vesicles. Patient 1 was on his 5th cycle of chemotherapy of Docetaxel, while the first cycle of Docetaxel was initiated in patient 2.

In patient 1, previous cycles were completed smoothly but this time within two days of receiving chemotherapy, he had complained of palpitation, weakness and extreme fatigue and had irregular pulse rate due to which he contacted his clinician who had advised the above tests.

The second patient complained of extreme chest pain, palpitation, sweating, generalized sense of unease

within 5 days of chemotherapy initiation due to which he had been advised to do the above tests.

Patient 1 was not on any other medication prior to chemotherapy except allopurinol which he had been taking for the past two years while patient 2 did not take any regular medication before his chemotherapy started.

On receiving the biochemical report, patient 1 were classified as TLS Grade 2 and patient 2 as TLS Grade 3 based on Cairo Bishop Grading System (4) (described in discussion). Patient 1 was having the LTLS in the form of hyperkalemia and hyperphosphatemia and mild clinical symptoms like palpitation, irregular pulse while patient 2 had LTLS in the form of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia along with severe palpitation and chest pain due to cardiac arrhythmia.

Both patients were hospitalized and shifted to ICU immediately and were started on IV fluids and allopurinol with continuous monitoring of urine volume as per TLS management guidelines. They were subsequently discharged on correction of dyselectronemia and when symptoms of palpitation and restlessness subsided. On follow-up found they were doing better and were scheduled to have their next cycles of chemotherapy.

CASE DISCUSSION

Although prostate cancer is one of the most common malignancies in male population, its early onset [below the age of 55] is rare, with only about 10% of new diagnoses occuring in this category.[5] Presence of hyperkalemia and hyperphosphatemia in prostate cancer may be due to:

- tumor lysis syndrome
- acute kidney injury
- chronic kidney disease
- adrenal dysfunction
- bone erosion linked with metastasis to the adrenal glands and bones.[6]

The patients had normal serum creatinine and slightly low urea and BUN and thus acute kidney injury or chronic kidney disease may be ruled out. They only had seminal vesicles metastasis with no bone or adrenal gland involvement. This is significant as it rules out adrenal dysfunction. It also increases the uniqueness of the cases as it is more common for a prostate cancer with bony metastasis to precipitate TLS but here TLS happened in both the cases without bony involvement.

Tumour lysis syndrome is diagnosed by Cairo Bishop Classification system which has separate criteria for laboratory and clinical classification [Table 3].

Table 3: Cairo Bishop Classification

Metabolic abnormality	Criteria for classification of laboratory tumour lysis syndrome	Criteria for classification of clinical tumour lysis syndrome	Comparison with patient 1 report	Comparison with patient 2 report
Hyperuricemia	>8mg/dl		2.9mg/dl	8.7mg/dl
Hyperphosphatemia	>4.5mg /dL		8mg/dl	9.72mg/dl
Hyperkalemia	>6 mEq /L	Cardiac dysrhythmia or sudden death caused by hyperkalemia	7.13mEq/L, palpitation, irregular pulse rate	6.17mEq/L, palpitation, irregular pulse rate
Hypocalcemia	<7 mg /dL	Cardiac dysrhythmia,suddendeath,seizure,nm irritability, hypotension, heart failure	7.5mg/dl	6.05mg/dl
Acute Kidney Injury (AKI)	NA	AKI(defined as creatinine>1.5* the upper limit of normal for patient's age and sex or avg urine output<0.5ml/kg/hr for 6 hrs	Absent	

According to Cairo-Bishop criteria, if a patient exhibit any two or more of the metabolic abnormalities, within three days before and seven days after chemotherapy, it is the case of LTLS. CTLS is present when LTLS is accompanied by any one of the clinical features.[6] However a limitation of this guideline is it does not take into account spontaneous TLS and TLS precipitated by radiotherapy.

Although rare, tumour lysis syndrome may be precipitated in prostate cancer post chemotherapy in case of a rapid surge of cell lysis, especially in bulky tumours and where metastasis has occurred.[7] Its incidence in prostate cancer is not exactly known due to lack of sufficient published case reports,[8] highlighting the relevance of this case. However, mortality rate as high as 75% has been found in published literature,[8] which may be based on how aggressive the tumour is, its degree of metastasis or simply because its rare and diagnosis is often delayed resulting in treatment delay culminating in death.[10]

The patient was classified based on Cairo-Bishop Grading System:[4]

- **Grade 0:** No laboratory TLS (LTLS)
- **Grade 1:** LTLS present, no clinical manifestations
- **Grade 2:** LTLS present, mild clinical manifestations (e.g., mild renal insufficiency, arrhythmia, or seizure)
- **Grade 3:** LTLS present, moderate clinical manifestations (e.g., moderate renal insufficiency, arrhythmia, or seizure)
- **Grade 4:** LTLS present, severe clinical manifestations requiring urgent intervention (e.g., life-threatening arrhythmia, seizures, or renal failure)

- **Grade 5:** Death

Patient 1 had potassium 7.13mEq/L and Phosphorus 8mg/dl and hence fulfilled the criteria of LTLS and patient 2 fulfilled all 4 criteria of L TLS while palpitation and irregular pulse rate and chest pain signifies cardiac arrhythmia which fulfilled the criteria of C TLS.

The rise of phosphorus and potassium in the patients can be explained as in TLS, due to the cellular lysis, these two intracellular ions get released into blood stream resulting in hyperkalemia and hyerphosphatemis. Hyperkalemia is the primary mediator of cardiac arrhythmia in TLS while hyperphosphatemia may contribute indirectly through hypocalcemia.

Serum calcium is also low in patient 1, though not <7mg/dl while in patient 2 it is below 7mg/dl. Low calcium is explained as secondary hypocalcemia due to hyperphosphatemia and due to chelation of calcium with phosphorus forming calcium phosphate. However calcium in patient 1 may not have fallen below 7mg/dl as it has been sometimes seen in prostate cancer, neuroendocrine cells of the prostate proliferate and stimulate secretion of parathyroid hormone related peptide thereby raising serum calcium.[11] PtTHrP (Parathyroid hormone related peptide) is more common in squamous cell tumours, breast and kidney cancer while in prostate cancer it occurs rarely in specific neuroendocrine subtypes Another more common explanation is docetaxel induced hypercalcemia which is the chemotherapeutic agent being administered to the patient.[12,13]

Serum uric acid is normally high in TLS as seen in patient 2 since it is a by product nucleic acid released from lysed cells.[4] But patient 1 was already on Allopurinol therapy which may explain his low uric acid levels.

In a review article,[14] on TLS cases in solid tumours, 16 were of genitourinary or urological cancers and only eight have been prostatic cancer. In all the eight reported cases, the presenting age of TLS was within 60 years to 80 years. In our case the age of presentation is 40 and 37 years highlights their uniqueness as we could not find any other publication of such young age of presentation.

CONCLUSION

Prostate cancer at the age of 40 is rare and TLS in prostate cancer even more so. The challenge of a standalone laboratory in reaching to clinical history and accelerating timely treatment is another highlighted importance of our case. This case series underlines the importance of linking clinical history with lab report and bridging the gap between clinics and diagnostics so that diagnosis of rare but critical cases can be made correctly on time and timely management may be provided to prevent TLS induced mortality.

As TLS is rare in solid tumours like prostate cancer its diagnosis may often be missed or delayed which may prove to be fatal. Many cases die within days as per published literature [9] . Unlike some other critical conditions with a short window period like MI and pre-eclampsia, TLS do not have any POCT available and therefore its diagnosis and subsequent management is reliant on correlating laboratory biochemical report with clinical history and symptoms. The chief challenge faced in these critical scenarios by a standalone reference lab is to procure timely history and correlate it with laboratory findings apart from ruling out potential errors in pre-analytical, analytical and post analytical phases to ensure timely release of report that can enable the patient to get urgent lifesaving treatment. According to the 2015 report on Improving Diagnosis in Health Care better communication between clinicians and lab professionals is paramount in improving diagnostics as delays or errors can cause grave harm to patient. In published literature, clinicians have cited difficulty in urgently contacting with standalone labs due to dilemma over whom to contact, how to contact which results in loss of time , while clinician number is mostly not provided with samples and hence lab consultants fail to contact them urgently. Based on our experience with this case, we propose the following information to be uploaded when samples of known malignancy patients on chemotherapy are being submitted for metabolic profile.

- Type of carcinoma (to understand its risk of developing TLS)
- Chemotherapeutic Agent Name (to see if it has more risk of TLS precipitation)
- History of Metastasis
- Tumour Grade (more bulky tumour has higher risk of TLS)
- History of Any Other Chronic Drug Intake (can influence values of parameters used for TLS classification)
- Previous Lab ID if any (to correlate with previous values of the same patient)
- Treating Physician Number (for faster communication and clinical correlation)

In India, so far, we know that there is no such standalone laboratory that have successfully implemented communication protocol for TLS cases. We already have a set protocol based on ISO 15189:2022 guidelines, where all critical results once validated by the consultant doctors, an auto generated mail and SMS is sent to the phone number and mail registered with the sample. Simultaneously the same mail is sent to the validating doctor confirming that the critical value has been informed. Unfortunately the registered number provided is almost never of the clinician which delays the relay of critical value information to them. We have planned to communicate and to encourage clinicians to provide their mobile number along with our proposed proforma in malignancy cases for quick correlation and communication for better and timely treatment.

Furthermore, after standardization and implementation of this protocol, we have planned to organise awareness and training programmes for physicians in form of CME's and newsletters by collaborating with clinics and hospitals.

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