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Development of tumor lysis syndrome (TLS): A potential risk factor in cancer patients receiving anticancer therapy

Mahmood Rasool[1]*, Arif Malik[2], Muhammad Saeed Qureshi[2], Riaz Ahmad[2], Abdul Manan[2], Muhammad Asif[3], Muhammad Imran Naseer[1] & Peter Natesan Pushparaj[1]*

[1]Center of Excellence in Genomic Medicine Research (CEGMR), King Abdulaziz University, Jeddah, Saudi Arabia; [2]Institute of Molecular Biology and Biotechnology (IMBB), the University of Lahore, Lahore, Pakistan; [3]Department of Biotechnology and Informatics, BUITEMS, Quetta, Pakistan; Mahmood Rasool - Email: mahmoodrasool@yahoo.com; Phone: +966-6401000; Fax: +966-6952521; Peter Natesan Pushparaj - Email: peter.n.pushparaj@gmail.com; Phone: +966-6401000; Fax: +966-6952521; *Corresponding authors

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Abstract:
Tumor lysis syndrome (TLS) is characterized by hyperuricaemia, hyperphosphatemia, hyperkalaemia, as well as hypocalcaemia due to the breakdown of tumor cells undergoing cancer therapy (chemo/radio). Therefore it is of interest to evaluate oxidative stress using selective biological markers [Malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione (GSH) and Catalase (CAT)] in TLS. We report the marked differences (statistically significant with control) observed among a selected set of biomarkers of oxidative stress (MDA = 8.66±1.37; SOD = 0.15±0.11; GSH = 2.25±.77; CAT = 0.76±.57) in TLS patients in addition to other conventional biomarkers. Moreover, correlation was investigated among the parameters of oxidative stress and other circulating biomarkers of TLS. Data suggest the use of SOD, MDA, and GSH as potential diagnostic biomarker for TLS with other biomarkers.

Keywords: Tumor lysis syndrome (TLS); hyperuricaemia; hyperphosphatemia; hyperkalaemia; hypocalcaemia; oxidative stress; MDA; SOD; GSH

Background:
Cancer is considered to be the second leading cause of death throughout the world **[1].** Tumor lysis syndrome (TLS) is one of the fatal complications of anticancer therapy. It occurs due to necrosis of the neoplastic cells and sometimes may also occurs spontaneously. Tumor lysis syndrome is a collection of metabolic abnormalities which results in the release of intracellular contents following the lysis of malignant cells and is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcaemia which results from massive cells death and release of intracellular uric acid, potassium and phosphate **[2].** The release of intracellular metabolites includes nucleic acids, protein, and phosphorus, potassium leads to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcaemia and uricemia **[3].** Electrolytes and metabolic disturbances can lead to renal insufficiency cardiac arrhythmias seizures and even death due to multiple organ failure **[2].**

Tumor lysis occurs in those neoplasms that have high cell turn over, large tumor burden and sensitivity to chemotherapy or radio therapy. Most of the cases of TLS occur after the treatment for haematological malignancies such as ALL and Burkitt's lymphoma followed by chemotherapy, radio therapy,

hormonal therapy or Immunotherapy. TLS occurs rarely in solid tumors but it is associated with breast cancer, small cell lung cancer, medulloblastoma and adenocarcinoma. Risk factors for TLS include high tumor burden, high rate of proliferation and disease that is highly responsive to therapy. The classification is based according to LTLS and CTLS criteria. Studies have indicated the usefulness of blood creatinine, uric acid, LDH, albumin, Na, K, Ca and P in diagnosis, prognosis and management of TLS **[2].**

Pathogenesis of TLS is complex and may affect multiple organs. Clinical consequences include cardiac arrhythmias, seizures, mental confusion, congestive heart failure, hypotension, tetany, fainting, renal failure and sudden death. Increased level of potassium from lysed tumor cells causes hyperkalemia that can cause cardiac arrhythmias. Hypocalcaemia observed is secondary to hyperphosphatemia and is due to formation of calcium phosphate crystals in renal tubules which can result in obstructive nephropathy due to nephro-calcinosis. Hypocalcemia can also cause seizures **[4].**

Methodology:

A total of 50 patients receiving anticancer therapy in different age groups (arbitrary) were involved in this study. We used 15 individuals with no systemic disease as controls. The samples were collected from patients at the Institute of Nuclear Medicine and Oncology (INMOL) Hospital, Lahore and Jinnah Hospital, Lahore, Pakistan. Informed consent was taken from all the individuals participated in this study. The study was also approved from the institutional ethical review committee.

Exclusion Criteria

Patients suffering from diabetes, hypertension, myocardial infarction or any other hepatic, pulmonary, pancreatic or renal diseases were excluded from the present study.

Sample Collection

5.0 ml of venous blood was drawn from healthy individuals (controls) and cancer patients undergoing anticancer therapy.

Blood Analysis

Blood was centrifuged at 4000 rpm for 10 minutes and serum was separated. Blood samples were collected into EDTA tubes.

Biochemical Analysis of Samples

The samples were processed and analyzed for the estimation of SOD, MDA, catalase and GSH by spectrophotometer method. Liver function tests (LFTs) and renal function tests (RFTs) were done by commercially available kits.

Results:

Table 1 (see supplementary material) summarizes all the results. Measurement of ALT showed that the value of ALT was significant and higher in case of tumor lysis syndrome. It is most often consequence of chemotherapy which causes the breakdown of hepatocytes resulting in the release of this enzyme into the circulation due to which the level of ALT increases. The value of AST was significantly higher in case of patient group. It is considered to be one of the indications of abnormal liver function tests which occur in case of TLS resulting mainly due to the induction of chemotherapy. The mean values of AST in case of control group is 24.06 ± 6.02, where as in case of patients of TLS it is 56.90 ± 17.34 IU/L which shows that AST is highly significant in case of patients suffering from TLS. The mean values of ALP in case of patient group is 375.12 ± 34.98 as compared to normal group in which it is 206.80 ± 4.50 which shows that there is a significant difference between the control and patient group. MDA is produced in case of Lipid Peroxidation process which occurs in TLS. It was observed that a significant increase in the level of MDA was present in case of patients suffering from TLS. The mean values for control group were 1.23 ±0.8 as compared with patient group in which mean values were 8.66 ± 1.37 which showed a significant increase in the level of MDA. Superoxide dismutase is one of the anti-oxidant enzymes. When measurement of SOD level was done in case of both these groups a significant difference was observed between the two groups. In case of control group the mean values were .476 ± .176, whereas in case of TLS patients mean values obtained were .15± .11 which showed a significant decrease in the level of SOD in case of patients undergoing TLS as a result of anticancer therapy. In case of hematological malignancies as well as solid organ tumors, the assessment of glutathione was done and it was observed that a highly significant difference were present. The mean values were 9.82 ± 1.09, whereas in the TLS patient group the mean values were 2.25 ± .772, which indicate that GSH is effective parameter of oxidative stress in cases of TLS. Catalase is common enzyme found in all living organisms. It is an anti-oxidative enzyme. The data displayed a significant difference is present between the values of the control and patient group. The mean values in case of control group is 4.35 ± .703, on the other aspect patient group showed the mean values .765 ± .579. Moreover, positive correlation was found among the parameters of oxidative stress and other circulating biomarkers of TLS **Table 2 (see supplementary material).**

Discussion:

Tumor lysis syndrome (TLS) is associated with the hematological cancer that is encountered in case of emergency by physicians. The symptoms of TLS are observed after the initiation of cancer treatment, although the symptoms of TLS without the cancer treatment have also been recognized. TLS exhibits variations in various tumor cases and it is independent of age and gender. The risk of TLS depends upon various parameters like burden of tumor, type of malignancy levels of lactate dehydrogenase (LDH) in serum and sensitivity of tumor to cancer treatment as well as involvement of bone marrow **[5].** 5-20% of cancer patients show TLS symptoms that represents serious complications often lead to death. It is necessary to recognize the risk factors of TLS as well as treatment in order to adequate management of tumor **[6].** Various metabolic abnormalities are appeared in patients, receiving cancer treatment, that are due to the rapid release of cellular metabolites like proteins, nucleic acids and electrolytes (phosphorus and potassium) from lysed malignant cells. These metabolites can lead to increase in uric acid (hyperuricaemia), high levels of potassium in blood (hyperkalaemia), increased concentration of phosphate (hyperphosphatemia), increased urea in blood (uraemia), and with or without low levels of calcium (hypocalcaemia) in blood. These metabolic abnormalities lead to acute renal failure (ARF), seizures,

arrhythmias and even death of the patient. Rapid turnover of malignant cells leads to considerable discharge of above mentioned intracellular contents into circulatory system.

Hyperkalaemia in TLS patients can cause serious problem like arrhythmias. Similarly hyperphosphatemia lead to arrhythmias, neuro-muscular irritability and seizures as well as precipitation as crystals of calcium phosphate in kidney that cause acute kidney injury (AKI) **[7].** Hyperuricaemia, similarly, induces AKI with or without the formation of crystals through the mechanisms of impaired auto-regulation, renal vasoconstriction, oxidation, inflammation and decreased renal blood flow **[8-10].** Through the process of excretion from the kidney, phosphate, urate as well as xanthine are removed from the body that may precipitate in any region of the renal collecting system. When the crystals of uric acid, calcium phosphate and xanthine are formed in the tubular system of kidney, they induce obstruction as well as inflammation **[11].** Moreover, the breakdown of tumor cells in TLS releases cytokines in the blood circulation that initiate inflammatory action in various organs that lead to organ failure, referred as systemic inflammatory response syndrome **[12-14].** In the present study the values of ALT and AST were significantly higher due to consequence of chemotherapy which causes liver damage. MDA levels were found high whereas SOD levels decreased significantly **(Table 1).** In Correlation matrix inverse correlation-ship was observed between MDA and SOD where as positive correlation-ship was observed between SOD and catalase **Table 2.**

Conclusion:

TLS is associated with anticancer therapy (chemo/radio) in cancer patients. Therapies in cancer patients are known to deplete SOD levels (an antioxidant agent in biological system) resulting in lipid peroxidation increase which is reflected by increased serum levels of MDA. An inverse relation was observed between MDA and GSH (GSH vs MDA, r = -0.534**) while a positive relation was observed between SOD and catalase (SOD vs CAT, r = 0.624*) as shown in **Table 2**. Thus, the use of biological biomarkers (SOD, MDA, catalase and GSH) in addition to other parameters (electrolytes, LFTs, BUN, WBCs, platelets, Hb and RFTs) in blood is promising in TLS diagnosis.

Conflict of interest:

The authors declared that they have no conflict of interest.

Acknowledgement:

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Supplementary material:

Table 1: Clinical parameters observed in patients and control groups

	Group	N	Mean ± SD	P value	Units
ALT	control	15	20.13±5.69	.000*	IU/L
	patients	50	86.88±34.46		
AST	control	15	24.06±6.02	.000*	IU/L
	patients	50	56.90±17.34		
ALP	control	15	206.80±4.50	.000*	IU/L
	patients	50	375.12±34.98		
MDA	control	15	1.23±0.8	.000*	nmol/mL
	patients	50	8.66±1.37		
SOD	control	15	.47±.17	.000*	ng/mL
	patients	50	.15±.11		
GSH	control	15	9.82±1.09	.000*	mg/dL
	patients	50	2.25±.77		
Catalase	control	15	4.35±.70	.000*	µmol/ mol of protein
	patients	50	.76±.57		
Creatinine	control	15	1.02±.14	.006	mg/dL
	patients	50	3.56±3.40		
BUN	control	15	12.93±1.94	.000*	mg/dL
	patients	50	33.96±5.57		
K^+	control	15	3.78±.55	.000*	mEq/L
	patients	50	6.10±.95		
Ca^{++}	control	15	8.95±.89	.000*	mg/dL
	patients	50	7.32±1.09		
phosphate	control	15	3.72±.54	.000*	mg/dL
	patients	50	5.81±.56		
Uric Acid	control	15	3.99±.64	.000*	mg/dL
	patients	50	10.47±1.48		
WBC	control	15	7.40±1.50	.000*	$x10^9/L$
	patients	50	54.39±29.08		
Hb	control	15	14.04±1.02	.000*	g/dL
	patients	50	9.48±1.53		
Platelets	control	15	219.07±23.21	.000*	$x10^9/L$
	patients	50	82.08±21.09		

*Significant (P<0.05)

Table 2: Correlation matrix of all the clinical parameters observed in the study

		ALT	AST	ALP	MDA	SOD	GSH	Catalase	Creatinine	BUN	K	Ca	Mg	phosphate	Uric Acid	WBC	Hb	Platelets
ALT	Correlation	1.000	.836**	.515**	.740**	-.400**	-.477**	-.500**	.417**	.594**	.574**	-.537**	-.673**	.564**	.547**	.618**	-.721**	-.468**
	P value	.	.000	.000	.000	.001	.000	.000	.001	.000	.000	.000	.000	.000	.000	.000	.000	.000
AST	Correlation		1.000	.498**	.698**	-.430**	-.399**	-.528**	.470**	.512**	.552**	-.427**	-.582**	.484**	.505**	.576**	-.690**	-.479**
	P value		.	.000	.000	.000	.001	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
ALP	Correlation			1.000	.695**	-.306*	-.515**	-.411**	.467**	.531**	.523**	-.394**	-.450**	.529**	.413**	.521**	-.438**	-.454**
	P value			.	.000	.013	.000	.001	.000	.000	.000	.001	.000	.000	.001	.000	.000	.000
MDA	Correlation				1.000	-.217	-.534**	-.415**	.492**	.595**	.614**	-.346**	-.587**	.652**	.532**	.573**	-.612**	-.385**
	P value				.	.083	.000	.001	.000	.000	.000	.005	.000	.000	.000	.000	.000	.002
SOD	Correlation					1.000	.407**	.624**	-.487**	-.519**	-.438**	.432**	.370**	-.334**	-.490**	-.443**	.415**	.604**
	P value					.	.001	.000	.000	.000	.000	.000	.002	.007	.000	.000	.001	.000
GSH	Correlation						1.000	.495**	-.626**	-.606**	-.580**	.270*	.462**	-.669**	-.647**	-.475**	.436**	.449**
	P value						.	.000	.000	.000	.000	.030	.000	.000	.000	.000	.000	.000
Catalase	Correlation							1.000	-.588**	-.632**	-.490**	.392**	.319**	-.390**	-.617**	-.453**	.561**	.602**
	P value							.	.000	.000	.000	.001	.010	.001	.000	.000	.000	.000
Creatinine	Correlation								1.000	.505**	.560**	-.296*	-.413**	.425**	.730**	.383**	-.500**	-.572**
	P value								.	.000	.000	.017	.001	.000	.000	.002	.000	.000
BUN	Correlation									1.000	.441**	-.389**	-.505**	.544**	.527**	.624**	-.562**	-.538**
	P value									.	.000	.001	.000	.000	.000	.000	.000	.000
K	Correlation										1.000	-.370**	-.499**	.615**	.495**	.388**	-.420**	-.432**
	P value										.	.002	.000	.000	.000	.001	.000	.000
Ca	Correlation											1.000	.513**	-.459**	-.342**	-.501**	.445**	.380**
	P value											.	.000	.000	.005	.000	.000	.002
Mg	Correlation												1.000	-.618**	-.502**	-.473**	.666**	.433**
	P value												.	.000	.000	.000	.000	.000
phosphate	Correlation													1.000	.552**	.522**	-.596**	-.346**
	P value													.	.000	.000	.000	.005
Uric_Acid	Correlation														1.000	.550**	-.635**	-.464**
	P value														.	.000	.000	.000
WBC	Correlation															1.000	-.482**	-.552**
	P value															.	.000	.000
Hb	Correlation																1.000	.482**
	P value																.	.000
Platelets	Correlation																	1.000
	P value																	.