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Interrelationship of anti-oxidative status and circulating biochemical markers in patients with cancer experience tumor lysis syndrome (TLS)

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Abstract

Tumor lysis syndrome is metabolic abnormality arises in response to anti-cancer treatment. It may develop in both pediatric or adult cancer and thought to be high risk oncologic emergency. Chemotherapy is one of the frequent method for the treatment of cancer patients. Fifty patients of TLS and Twenty age and sex-matched clinically apparently healthy individuals were eligible for inclusion in the study. 5 ml blood sample were taken and subjected to centrifuge at 4000-5000rpm for 10-15 minutes for the separation of serum. The level of MDA, SOD, CAT, GSH, VIT A, VIT C, VIT E, Nitric oxide (NO), Neuraminidase, Electrolytes (Na^+, K^+) TNF-alpha and IL-2 were estimated. The MDA level in TLS patients was increased (6.35±2.16) as compared to control (2.57±0.81) and statistically significant (0.026<0.05). SOD level decreased in TLS patients (0.954±0.065) as compared to healthy individuals (1.38±0.16) and statistically significant (0.003<0.05). TNF-alpha level in TLS patients was elevated (36.35±4.26) as compared to control (24.98±3.78) and statistically significant (0.032<0.05). IL-2 level was also raised in TLS patients (331.55±0.24) as compared to healthy ones (263.17±1.97). Nitric oxide and Neuraminidase level in TLS patients was higher (41.26±2.54 and 8.06±2.26 respectively) as compared to control group (17.78±2.67 and 7.26±2.16 respectively). Present study showed the relationship present between Oxidative stress, Vitamins, Electrolytes, IL-2, TNF-alpha and TLS. These results confirm a perfect sketch regarding circulating biomarkers and lipid peroxidation. Increased level of MDA as a biomarker of lipid peroxidation, IL-2 and TNF-alpha is the cause for the progression of the disease.

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Introduction

Tumor lysis syndrome is a metabolic disorder arises in response to anti-cancer treatment spontaneously. It arises when huge number of rapidly proliferating cancerous cells mainly leukemia and lymphoma are lysed through cytotoxic therapy such as radiations or chemotherapy. Malignant cells release their contents into the systemic circulation due to which they accumulate in the body instead of being eliminated and difficult for the body to manage. Severe metabolic disorders arises due to the release of these intracellular components which leads to lethal complications such as hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia. Cytokines are released due to tumor lysis that causes systemic inflammatory response syndrome and multi-organ failure (Hijiya *et al*., 2005; Nakamura *et al*., 2009 and Soares *et al*., 2009). The prevelance of tumor lysis syndrome (TLS) varies substantially depending on the disease. It is observed in acute leukemias with high tumor burden, high cell destruction, sensitivity to chemotherapeuticals and high leukocyte count and in Burkitt type non-Hodgkin lymphomas. However, TLS may occur unexpectedly in other cases in the low risk group. Therefore, one should be careful in the follow-up of all cancer patients especially during the first one week after treatment is started (List *et al*., 1990; McCroskey *et al*., 1990 and Yang *et al*., 1999). 20-50% of the cases may result in mortality, if the diagnosis of TLS is not made accurately and treatment is not started (Bose and Qubaiah, 2011). Different anti-cancer treatment methods exist such as cytotoxic drugs, biological substances, corticosteroids, hormones and radiation therapy that leads to the occurrence of TLS. Rarely, TLS spontaneously occurs before prophylactic therapy has been started (Cairo and Bishop, 2004). TLS is categorized into two groups, Laboratory TLS defined by the abnormalities in serum concentrations of uric acid and electrolytes while Clinical TLS described by the symptomatic complication of metabolic abnormalities (Coiffier *et al*., 2008). Clinical symptoms of TLS arises after 12-72 hours of the initial treatment including seizures, renal failure and cardiac arrhythmias (Hochberg and Cairo, 2008). The most recurrently appearances of tumor lysis syndrome that leads to many clinical imbalances are hyperuricemia and its related consequences. Excretion and catabolism of intracellular nucleic acid leads to the hyperuricemia. Rapid release of the intracellular phosphate leads to the formation of the hypophosphatemia (Locatelli and Rossi, 2005 and Yarpuzlu, 2003). Tumor bulk and type, type of chemotherapy used in the treatment and preceding clinical conditions like dehydration or acute kidney disease are the factors related to the progress of TLS (Cairo and Bishop, 2004; Arrambide and Toto, 1993 and Altman, 2001). High mitotic rate and high response therapy tumors are the frequent sites of TLS (Hussain *et al*., 2003; Rostom *et al*., 2000; Anderson and Files, 2002; Benekli *et al*., 1996 and Benekli *et al*., 1995). Hematologic and non-hematologic carcinomas and acute leukemias like acute lymphoblastic Leukemia (ALL) and highly aggressive lymphomas such as Burkitt's lymphomas are more prone to TLS (Davidson *et al*., 2004 and Vaisban *et al*., 2003). Cancerous cells are greater in amount during the time of chemotherapy treatment that's why it has a greater risk for the development of TLS (Seki *et al*., 2003 and Hagemeister and Huen, 2005).Spontaneous TLS with solid tumor is found in Breast cancer, gastric cancer, germ cell tumor, squamous cell lung carcinoma and metastatic castrate prostate cancer (Lin *et al*., 2007; Pentheroudakis *et al*., 2001; Woo *et al*., 2001; Sklarin and Markham, 1995 and Crittenden and Ackeman, 1970). Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) are the most effective enzymatic antioxidants (Mates *et al*., 1999). In case of neoplastic cells, elevated level of ROS and changed activities of both enzymatic and non-enzymatic antioxidants are interrelated to each other (Sies *et al*., 2005).

Therefore, the aim of this study is to investigate or correlate the relationship between anti-oxidative and circulating biochemical markers in tumor lysis syndrome (TLS) patients.it will also examine the local cytokine production in situ unbiased by manipulation of these cells in tissue culture. This will be accomplished by performing PCR on mRNA derived from these specimens.

Materials and methods

Source of data

I. Fifty patients of Tumor Lysis syndrome (TLS) were eligible for inclusion in the study at Jinnah Hospital Lahore. Detailed history, clinical complications if any habits in particular smoking and tobacco chewing were collected from subjects of the study, by giving them a questionnaire. Clinical diagnosis of the patient was also be taken into consideration.

II. Twenty age and sex-matched clinically apparently healthy individuals were included as controls.

Method of collection of data

Blood samples were collected with aseptic precaution. Informed consent from subjects was obtained before collection of blood samples.

Sample and sampling technique

Blood samples of Patients and controls were collected and processed. 5ml blood were collected in EDTA-Vaccutainers and centrifuged.

Chemicals

All chemical reagents of analytical grades were purchased from Sigma Chemical Co. (St. Louis, Mo, USA).

Following parameters were estimated

Estimation of reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), electrolytes sodium (Na+) and potassium (K+) concentration, Nitric oxide (NO), neuraminidase, interleukin-2 and tumor necrosis factor (TNF-alpha). Estimation of vitamins (vit A, C and E). MDA was estimated by the method of Ohkawa *et al*., (1979). SOD was estimated by the method of Kakkar *et al*., (1984). Activity of CAT was estimated by the method of Aebi, (1984).

Results

The data represented in the above table shows the clear cut picture of the different parameters estimated in the patients suffering from tumor lysis syndrome (TLS). When the serum electrolyte balance was measured in the patients of tumor lysis syndrome, it was observed that sodium level (Na+) level increases (28.26) as compared to healthy individuals (21.26) and statistically significant (0.02<0.05).

Potassium level in the TLS patients was (13.26) while in healthy individuals (14.26) and statistically significant (0.03<0.05).

Variables	*Control (n=20)*	*Subjects (n=50)*	*P<0.05*
Na (mg/L)	21.26±4.26	28.26±3.26	.0254
K (mg/l)	14.26±3.26	13.26±4.26	.0314
Vit.A(µg/ml)	188.26±91.72	102.20±14.26	.026
Vit. E (µg/ml)	7.26±0.94	4.26±1.25	.01564
Vit.C(µg/ml)	2.41±0.24	1.66±.045	.0165
MDA (nmol/ml)	2.57±0.81	6.35±2.16	.0265
GSH (µg/dL)	7.93±0.28	3.24±1.25	.0024
SOD (µg/dL)	1.38±0.16	.954±.065	.0035
CAT (µg/dL)	4.33±0.37	1.05±.065	.0064
IL-02 pg/ml	263.17±1.97	331.55.±.024	.021
TNF-α (pg/ml)	24.98±3.78	36.35±4.26	.0321
AOPPs	1.29±0.091	1.334±.265	.0825
NITRIC OXIDE (NO)	17.78±2.67	41.26±.254	.054
NEURAMINIDASE	7.26±2.16	8.06±2.26	.054

When the vitamins level was observed, it was noticed that vitamin A level in TLS patients decreases remarkably (102.20) as compared to control (188.26) and statistically significant (0.026<0.05). Vitamin E level in TLS patients was (4.26) and in healthy individuals (7.26) and statistically significant (0.015<0.05). Serum Vitamin C level decreases in patients (1.66) as compared to control (2.41) and statistically significant (0.016<0.05). When different parameters of the oxidative stress were measured, it was observed that MDA level in the patients was (6.35) as compared to control objects (2.57) and statistically significant (0.026<0.05). GSH level in TLS patients decreases (3.24) as compared to healthy individuals (7.93) and statistically significant (0.002<0.05). SOD level decreases in patients (0.954) as compared to control (1.38) and statistically significant (0.03<0.05). Catalase level in TLS patients was (1.05) while in healthy objects (4.33) and statistically significant (0.006<0.05). When the interleukin-2 level was measured in the TLS patients, it was observed that it increases remarkably (331.55) as compared to healthy objects (263.17) and statistically significant (0.021<0.05). TNF-alpha level in TLS patients was (36.35) while in healthy individuals (24.98) and was significant (0.03<0.05). When AOPPs level was measured in TLS patients, it was observed that it increases (1.334) as compared to healthy individuals (1.29) and statistically non-significant. Level of Nitric Oxide (NO) in TLS patients increases remarkably (41.26) as compared to control (17.78). Neuraminidase level in the TLS patients increases (8.06) as compared to healthy objects (7.26) and statistically significant (0.05).

Discussion

As the population continues to age, the incidence and risk of older adult patients developing cancer greatly increases. About 25% of new cancer diagnoses occur in those aged 65-74 years, whereas an additional 22% occur in those aged 75-84 years (Hanson and Muss, 2010). Statistics show that 60% of cancers and 70% of cancer deaths occur in patients older than age 65 (Bond, 2010). Leukemia and lymphoma diagnoses are among the less common but often highly morbid malignancies of later life.

TLS is a rapidly developing oncologic emergency characterized by electrolyte and metabolic disturbances that are fatal without timely identification and management. Patients present with hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia. Electrolyte disturbances can cause acute renal and multisystem organ failure. Patients at highest risk for tumor lysis syndrome (TLS) often are diagnosed with bulky, rapidly proliferating hematologic tumors, such as acute leukemia and non-Hodgkin lymphoma (Kaplow and Hardin, 2007). Patients with solid tumors, such as mediastinal masses which are highly sensitive to chemotherapy, also may develop TLS, although it is more common in patients undergoing treatment for leukemia and lymphoma. TLS occurs from the effect of chemotherapy or radiation on rapidly dividing cells. Patients with elevated lactic dehydrogenase (LDH), dehydration, and renal insufficiency are at greatest risk for developing TLS (Brant, 2002).

Advances in cancer treatment, such as those in bone marrow transplantation, require the use of high-dose chemotherapy, which may demonstrate an increase in the incidence of TLS. Of particular importance in understanding the immune response to cancer is the specific pattern of cytokines produced locally, since immunotherapy is often directed towards altering these patterns. To investigate the cytokine response in small tumor biopsy specimens, we have adapted the PCR technique to determine the pattern of expression of 11 cytokines. This was accomplished by comparing the immune response in a malignant tumor of the epidermis, BCC, to that of a benign growth of the epidermis, SK.

In comparing the cytokines produced by T cells, we noted two strikingly distinct patterns. IL-4 and IL-10 were the dominant cytokine mRNAs noted in BCC specimens whereas, in contrast, IL-2 and IFN-γ were identified as the predominant cytokines in SK.

The significance of the damage inflicted upon biological systems by ROS cannot be overestimated, as they have been implicated in numerous disease processes, including inflammation, degenerative diseases, and tumor formation and involved in physiological phenomena, such as aging and embryonic development. The dual nature of these species with their beneficial and deleterious characteristics implies the complexities of their specific functioning at a biological site and the difficulties in establishing appropriate intervention procedures to treat ROS-related diseases. Their detection using chemical and immune histochemical methodologies is, therefore, essential to elucidate their exact mechanisms of activity and may allow development of antioxidant intervention strategies leading to reduction in diseases associated with oxidative stress. Such strategies may delay age-related degenerative diseases and enhance the quality of life, particularly in the later years.

The SOD model for cancer would lastly predict that addition of SOD activity to tumor cells would enable them to reacquire at least some of the characteristics of normal cells (such as growth control). One cannot expect that the addition of SOD to tumor cells would enable the tumor cell to become completely normal, because some of the dam age sustained by these cells is likely to be irreversible. This prediction is at present difficult to test for lack of a com pound with SOD activity that can penetrate into the cell. Native SOD, either of the Cu-Zn or Mn form, does not enter the cell due to its large molecular weight. For this reason, it was not expected that SOD itself would affect tumor growth.

One of the main problems with these compounds to date has been their lack of solubility and difficulty in entering the tumor. These compounds, as well as adding SOD to liposomes, hold promise for cancer therapy in the future.

Conclusion

Conclusion of the present study is that MDA level in TLS patients was elevated due to the lipid peroxidation, while other oxidative stress parameters decreases (SOD, CAT, GSH).Elevation of MDA, IL-2, TNF-alpha are the cause for the progression of disease.

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Conflict of interest

There is no conflict of interest

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