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STUDY OF SERUM LACTATE DEHYDROGENASE LEVELS IN LYMPHOMA PATIENTS IN A TERTIARY CARE HOSPITAL.

Dr. Beshwanth Chowdary V[1*], Dr. D. Bhavya[2], Dr. K. Divija[3], Dr. C. Venkata Harish[4]

[1*]Assistant Professor, Department of Pathology, Government Medical College (RIMS), Kadapa.
[2]Assistant Professor, Department of Pathology, Government Medical College (RIMS), Kadapa.
[3]Assistant Professor, Department of Pathology, Government Medical College (RIMS), Kadapa.
[4]Assistant Professor, Department of Pathology, Government Medical College (RIMS), Kadapa.

***Corresponding Author:** Dr. Beshwanth Chowdary V
*Assistant Professor, Department of Pathology, Government Medical College (RIMS), Kadapa.

INTRODUCTION

Lymphoma is a neoplasm of clonal proliferation of lymphoid cells. It is divided into Hodgkin lymphoma(HL) and non-Hodgkins lymphoma(NHL). HL usually manifests as a nodal disease, usually involving cervical, axillary, and inguinal nodes involving a single group. NHL develops in nodes as well as extra-nodal locations like gastro intestinal tract and oral cavity. [1].

Lactate dehydrogenase (LDH) is an oxidoreductase that aids in interconversion of pyruvate and lactate. LDH has five subtypes which are organ specific. LDH type 2 is mainly found in lymphoid tissues. [3,4]

LDH estimation is a very inexpensive test which can offer evaluation of disease extent in patients with lymphoma. [5, 6] Damage to the cell membrane during high stress related to rapid cell division causes LDH release in to the serum and rise in the level of LDH is seen in various malignancies. [7]

The malignant cells utilize almost as much as five times the glucose compared to normal tissues, converting it into lactate and shunting it into hexose monophosphate shunt. The increased levels of LDH in malignancies may reflect increased production of LDH by cancer cells . LDH is one of the components of Lymphoma International Prognostic Index. LDH serum level is considered a valuable biochemical parameter in the evaluation of disease extension in both HL as well as NHL.[8]

Lymphoma is broadly divided into Hodgkins lymphoma(HL) and Non Hodgkins lymphoma (NHL)categories [9, 10] During the past decades incidence of highly aggressive NHL cases is on the rise. NHL has a good chemosensitivity and early detection and evaluation of disease burden is a key factor in patient treatment and prognosis.

LDH is not a very specific for lymphoma. But it is a good marker for assessing disease activity and cellular proliferation and it can be used as an inexpensive tool for both diagnosis and screening of suspected lymphoma cases. Biopsy is the gold standard for detection of lymphoma. LDH can provide a strong adjunct to clinical and radiological information. [11,12]

REVIEW OF LITERATURE

Aviles *et a*l conducted a research on 162 patients suffering from NHL from 1980 to 1982. A bad prognosis was associated with high levels of LDH. It was also associated with poor complete remission and short survival rates. [18]

A retrospective study was conducted by Hisamitsu S *et al* for a group of 121 patients with Ann Arbor stage I-II head and neck non-Hodgkin's lymphoma. LDH levels were found to be a

significant prognostic variable. [19]

Pan *et al* conducted an immunohistochemical study to explore the relationship between LDH isoenzyme elevation and cell proliferation. They evaluated the expression of LDH isoenzymes and B and T lymphocytes immunocytochemically. T lymphocytes showed minimal staining for M-type LDH while on the other hand a strong staining for H-type LDH,;Also, B lymphocytes depicted little staining for M-type LDH. On activating T cells, M-type LDH would rise as cells moved to early stages of cell cycle. When maximum number of T cells were present at S/G2/M phase of the cell cycle, the staining intensity hit its maximum limit. The expression of M-
type LDH reduced when T cells went back to resting state. This study was useful for quick evaluation of the proliferating fraction of neoplastic cells in the human body.[20]

Pirc-Danoewinata *et al* conducted a study on malignant NHL to correlate clinical data and chromosomal aberrations in 70 adult patients with newly diagnosed NHL followed for a median of 20 months. Clonal aberrations were detected in 68/70 patients. Aberrations of chromosome 7 (n = 21) occurred in all histological subtypes together with aberrations of chromosome 3 and of the short arm of chromosome 17.This was linked to high LDH levels and low survival rates.

Anomalies of the long arm of chromosome 13 (n = 10) were found in patients with high grade B-cell lymphomas and bulky disease. In t (14; 18) (q32; q21) bearing lymphomas (n = 27), distinct patterns of additional aberrations were observed in low grade and high grade lymphomas: trisomy 3 and trisomy 18 occurred concomitantly in high grade lymphomas (n = 6, $p < 0.001$) as well as aberrations of 1q, 5q, 6q and +der (18) (q21). In conclusion, cytogenetic analysis provides information about the complexity of genetic changes in NHL. These changes act not only as indicators of disease activity, but influence clinical outcome as demonstrated by their stringent correlation to the International Index and might reveal more general rules of tumor growth and spreading. [22]

Virijevic *et al* conducted a retrospective study for a period of 10 years to investigate prognostic clinical and laboratory factors significant for the outcome of patients with mucosa associated lymphoid tissue (MALT) lymphoma.

They studied 87 patients who had lymphoma of MALT type. Of these patients 50 were with non GI localization and 37 with GI localization. They have estimated LDH levels and found it to be of prognostic significance. They have seen that elevated LDH level was a poor prognostic factor associated with spread to non GIT sites. [23]

Huang *et al* retrospectively collected the clinicopathological features and radiological data of 23 patients with pulmonary MALT lymphoma from January 2001 to December 2010 . Among the 23 patients only 1 patient had elevated LDH levels. The study concluded that Pulmonary MALT lymphoma has increased incidence in females and tends to be restricted to the lungs. Most importantly on initial diagnosis, the LDH levels were found to be normal. [24]

Forty cases of primary breast lymphoma were retrospectively studied by Yang *et al* and data was analyzed to study the clinico-pathologic features and prognosis of primary lymphoma of breast. There was elevation in levels of LDH in 9 out of 40 cases. Also, in 27 cases having diffuse large B-cell lymphoma, disease-free survival rates and five year survival was found to be 48.0% and 36.0%, respectively. The level of LDH was considered to be of prognostic significance. [25]

A retrospective study on Primary gastric lymphoma (PGL) was done between 2003 to 2015 with 165 patients at West China Hospital. The clinical features, treatment, and follow-up information were analyzed. 108 patients having diffuse large B-cell lymphoma (DLBCL) and 52 patients having mucosa-associated lymphoid tissue (MALT) lymphoma were enrolled in this study. High levels of LDH was directly associated with poor prognosis and it proved be an independent predictor of survival rates. [29]

AIM AND OBJECTIVES.

Evaluation of LDH enzyme levels in lymphoma patients.

Assesment and analyses of significance of LDH estimation in lymphoma patients.

MATERIALS AND METHODOLOGY

LDH levels of 110 patients (HL+NHL) was collected and analysed. The clinical stage of lymphoma at presentation was documented.

study setting

The study was conducted in the Department of Pathology, Government Medical College (RIMS), Kadapa. The medical records section was accessed for patient details and investigation profile.

Study Period: 3 years. 2017-2020

Sample size: 110 patients

Inclusion criteria:

Diagnosed Lymphoma cases with LDH levels estimated at time of diagnosis.

Exclusion criteria:

Patients without LDH estimation.

Study design: A Retrospective Study

Data analysis

The data was analyzed by using Microsoft SPSS (Statistical Package for Social Sciences)version 12.

OBSERVATIONS AND RESULTS

We have collected the data of 110 patients out of which 26 were HL and 84 were NHL.
In HL the mean age of presentation was 50.0122 years, while in NHL it was 50.1923 years. The age range of HL was 2 years to 78 years.
And for NHL was 7 years to 84 years.

Table 1. Distribution of HL and NHL across age groups.

	<20years	20-40 years	40-60years	60-80 years	80-100 years	TOTAL
HL	8	6	8	4	0	26
NHL	5	13	28	37	1	84
	13	19	35	41	1	110

Under the category of HL we had 10 female 16 male patients, and under NHL we had 40 female and 42 male patients.

Table 2. Distribution of Hodgkin and Non-Hodgkin's lymphoma across sexes.

	FEMALE	MALE	total
HL	10	16	26
NHL	40	44	84
	50	60	110

In HL we have 16 patients in stage 1, 8 patients in stage 2, and 2 patients in stage 4.
In NHL, we had 28 patients in stage 1, 18 patients in stage 2, 17 patients in stage 3, and 21 patients in stage 4.

Table3. Distribution of HL and NHL cases among stages.

	STAGE 1	STAGE 2	STAGE 3	STAGE 4
HL	16	8	0	2
NHL	28	18	17	21

In HL we have 7 patients with LDH levels below 200U/L, 15 patients having LDH in the range of 200-400U/L, 4 patients with LDH in the range of 400-600U/L.
In non-Hodgkin's lymphoma we had 13 patients with LDH levels below 200, 40 patients having their LDH levels varying between 200-400U/L(Majority(28)were stage I), 11 patients with LDH levels between 400 to 600U/L. Among patients who had LDH levels greater than 600U/L, majority (20) were stage IV disease.

Table 4. Levels of LDH in NHL and HL

LDH levels	NHL	HL
<200 U/L	13	7
200-400 U/L	40	15
400-600 U/L	11	4
>600 U/L	20	0
	84	26

The mean LDH level in NHL was 384.2 U/L and HL was 289.5U/L. The standard deviation in NHL was 264.9U/L in HL was 121.7U/L. The range of LDH in NHL was 136-1614U/L. Range of LDH in HL was 28-568 U/L

Table 5: Mean levels of LDH with standard deviation

Type of lymphoma	Mean LDH(U/L)	Standard deviation	Minimum	maximum
NHL	384.2	264.9	136	1614
HL	289.5	121.7	28	568

We found a statistically significant correlation between the level of LDH and the stage of lymphoma, especially in NHL cases. The LDH levels were in general lower in cases of HL and higher in NHL. The majority of cases of both of both HL and NHL were having an LDH level of 200-600U/L at presentation. Majority of Stage 4 cases also presented with a LDH level of greater than 600U/L in NHL. Majority of HL cases presented with 200-400U/L LDH levels. Stage 4 cases were seen with more frequency in NHL (21 NHL cases). In HL cases, only 2 were stage 4.

DISCUSSION

In lymphomas it is generally recognized that LDH is elevated at the time of presentation. As it is a very inexpensive and readily available test in almost every center, LDH level is evaluated for most of the patients with clinical suspicion of lymphoma. We looked into the presenting LDH levels of histopathologically confirmed cases of lymphoma. As it would be generally assumed, the LDH level should represent the level of cellular proliferation and activity because it is a metabolic enzyme. Many studies have reported increased LDH level with increased proliferative activity of cells.[4]]

Pan et al showed that LDH level is proportional to the cellular proliferation. [4] Rodriguez et al observed that there was a rise in LDH levels in advanced stages of lymphoma patients.[20] Hernadez et al analyzed LDH levels in lymphoma cases and have found LDH levels greater than 320 associated with advanced stage and extra-nodal involvement.[21]

Higher levels of LDH were found in NHL when compared to HL cases, and majority of cases were having LDH level between 200-400U/L (n=55). Also, majority of patients were in stage 1 in both NHL and HL group. There was no statistically significant correlation between the LDH level and the lymphoma subtype. There was significant positive correlation between stage of disease and LDH level in NHL sub group.

CONCLUSION

The NHL group showed incidence of lymphomas predominantly above 40 years of age. The HL group had an even distribution across ages. The LDH levels were significantly higher in NHL group. Majority of the NHL and HL cases presented at stage 1. The majority of patients had an LDH level of 200-400U/L in both groups of NHL and HL. We found a statistically significant association between the stage of lymphoma and levels of LDH. In patients with higher stage disease and more disease burden the LDH level was high. In conclusion LDH can be used as a good cost effective screening marker in suspected lymphoma cases and also as a marker for estimation of disease burden in diagnosed cases.

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