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Study of Selenium Concentration in Patients with Newly Diagnosed Non-Hodgkin's Lymphoma

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This study was designed to examine selenium concentrations in patients with newly diagnosed Non-Hodgkin's Lymphoma (NHL) and the possible association between the levels of this trace element with clinical features of the disease. Also, to test the hypothesis that selenium concentration at presentation would predict for response to treatment. This study was carried out on fifty-patients with newly diagnosed NHL and 25 control subjects, blood samples were taken for measurement of selenium by spectrometry. In comparison to the control subjects the serum selenium level was significantly lower with NHL with a mean of 0.033 (SD, 0.1) vs 0.81 (SD, 0.05), $p<0.001$. The mean serum selenium was significantly lower in patients with poorer performance status ($p = 0.03$) and in patients with advanced stage ($p = 0.02$), but there was no significant relation to the aggressiveness of the disease. Serum albumin was the only parameter that showed a significant positive correlation with serum selenium. There was a trend for serum selenium level to be higher in patients who achieved CR, but the difference was not statistically significant ($p = 0.1$). Selenium may play a role in the pathogenesis and prognosis of patients with NHL. In this study; the level of selenium was found inversely associated with the clinical stage of the disease and the performance status and may predict for the response to treatment in aggressive lymphoma. The possible utility of measuring serum selenium in NHL deserves further evaluation in clinical trials.

Key words: Selenium, Non-Hodgkin's Lymphoma (NHL) trace element, pathogenesis, prognosis

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INTRODUCTION

Selenium is an essential trace element for most living organisms. Much scientific attention is currently focused on the possible role of selenium as an antineoplastic drug and the hypothetical involvement of this trace element in the etiology of human cancer (Patrick, 2004).

Epidemiological and experimental studies have suggested that selenium possesses anticarcinogenic properties (Combs and Gray, 1998; El-Bayoumy *et al*., 1991; Stadtman, 1996). The mechanisms by which selenium exerts its chemopreventive activity is unknown; however, several plausible explanations have been put forward including the role of selenium in inducing cell cycle arrest (Sinha *et al*., 1996), DNA strand breaks (Lu *et al*., 1994; Wilson *et al*., 1992) and apoptosis (Lanfear *et al*., 1994; Kim *et al*., 2001).

A number of case control studies were performed from the early 1980s onward. In such studies, selenium levels in blood, serum or other indicator organs of healthy subjects are compared with those of cancer cases or of subjects who developed cancer at some time after samples were taken. In the majority of these studies, selenium levels have been found to be lower in a variety of cancer diagnoses compared to both matched and unmatched controls (Sanz Alaejos and Diaz Romero, 1993; Li *et al*., 2004).

More recently the role of selenium in the prevention of cancer has been established by laboratory experiments, clinical trials and epidemiological data. Most of the effects are related to the function of selenium in antioxidant enzyme systems. Animal data, epidemiological data and intervention trials have shown a clear role for selenium derivatives in both, prevention of specific cancers and antitumorigenic effects in post-initiation phases of cancer (Soriano-Garcia, 2004; Aboul-Fadl, 2005).

In vitro study of the effect of selenium compounds on lymphoma cells revealed that the selenium compounds methylseleninic acid and selenodiglutathion induce cell death in lymphoma cell lines and primary lymphoma cultures (Last *et al*., 2006). Also, sodium selenite could induce apoptosis in murine b-lymphoma cells. This was associated with inhibition of protein kinase C, nuclear factor κB and inhibitor of apoptosis protein (Gopee *et al*., 2004).

Selenium concentrations in patients with newly diagnosed lymphoid malignancies were significantly lower in patients than in control subjects. However, when only patients with localized disease were compared to controls, no significant difference in serum selenium concentrations was observed. Clinical stage was inversely associated with selenium levels (Avanzini *et al*., 1995).

Selenium concentration at diagnosis was reported to be independently predictive of both treatment response and long-term survival in patients with aggressive non-Hodgkin's lymphoma. In a group of 99 assessable patients, response to first treatment was 54% in the lowest serum quartile compared with 88% in the highest quartile, with a lower overall survival in patients with lower serum selenium (Last *et al*., 2003).

Pretreatment serum selenium concentration correlated with response to treatment in a group of 51 patients with cutaneous T-cell lymphomas and proved to be independent predictive of outcome in a multivariate analysis that included clinical variables as cofactors (Deffuant *et al*., 1994).

These observations led us to examine the serum levels of selenium in patients with newly diagnosed NHL and the possible association between the levels of this trace element and some clinical features of the disease. This study was undertaken also to test the hypothesis that serum selenium at presentation would predict for response to treatment.

MATERIALS AND METHODS

This study was carried out on fifty-patients with newly diagnosed non-Hodgkin's lymphoma, attending the Out Patient Medical Oncology Clinics at Mansoura Oncology Center. The diagnosis of NHL was based on a surgical specimen/excisional lymph node biopsy providing enough material for pathological evaluation and classification according to the WHO. Patients were recruited during the period from May 2006 to January 2007.

Patients were subjected to:

- Thorough history taking and clinical examination, including assessment of the performance status according to the Eastern Cooperative Oncology Group (ECOG)
- Complete blood count
- Routine blood chemistry including ESR, LDH
- CT-scan of the thorax, abdomen and pelvis
- Bone marrow aspirate and biopsy

Exclusion criteria:

- Past history of malignant disease
- Concomitant advanced organ failure
- Associated mal-absorption
- Patients who had been previously treated

In addition 25 healthy volunteers were recruited to draw blood samples as control for the blood selenium level following the same procedures used in the patients. The control volunteers were selected so that they match the cases for age and sex.

Assessment of the response: Response status was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). All studied cases with low grade NHL presented at an advanced stage not amenable for curative treatment. While the 38 cases with aggressive NHL included 35 patients fit for curative treatment, one patient of them lost follow up before assessment of the response. So, only 34 patients were evaluable for response.

Evaluation of response was done by clinical evaluation in addition to repetition of the appropriate laboratory and radiological investigations after 4 cycles of chemotherapy.

Selenium concentration measurement: One milliliter whole blood was transferred into 50 mL Pyrex beaker followed by addition of 5 mL nitric acid. A watch glass was placed on the top of the beaker. This mixture was heated and near dryness, 1 mL perchloric acid was added. The digestion was continued, it was complete with the appearance of white fumes of perchloric acid and stored in 10 mL acid treated polyethylene tube (Vanloon, 1987). Measurement of selenium was carried out in triplicate with the use of Perkin-Elmer 2380 Atomic Absorption Spectrometer in Analytical Chemistry Department, Faculty of Science, Mansoura University.

Statistical analysis: All statistical analyses were conducted with SPSS program, version 10. Descriptive statistics with mean, Standard Deviation (SD) and range were used for quantitative variables, while number and percent were used for qualitative variables. For analysis of the differences in proportions, Chi Square test was used. Pearson correlation analysis was used to examine the relationship between blood selenium levels and age in the study population and between selenium and the remaining hematologic variables in patients. Unpaired Student's t-test was used for comparisons between means. A two-tailed $p \leq 0.05$ was considered significant in all procedures.

RESULTS

This study was carried out on 50 patients with Non-Hodgkin's Lymphoma (NHL) and 25 controls. Patient and control groups are matching for age (mean 47 vs. 43 years, p = 0.14) and sex (male 56% vs. 48 %, p = 0.5) (Table 1). The presentation blood selenium concentration level was normally distributed for the 50 patients as well as for the control. In comparison to the control the blood selenium level was significantly lower in patients with NHL with a mean of 0.33 (SD, 0.1) vs. 0.81 (SD, 0.05), $p<0.001$.

Table 1: Characteristics of studied cases

Characteristics	No.	(%)
Sex		
Male	28	56.0
Female	22	44.0
Symptoms		
Absent	30	60.0
Present	20	40.0
Performance status (ECOG)		
0	17	34.0
1	19	38.0
2	12	24.0
3	2	4.0
Stages		
1	6	12.0
2	12	24.0
3	14	28.0
4	18	36.0
Pathological grade		
Low grade	12	24.0
Aggressive	38	76.0
	Mean±SD	Range
Age (years)	47.00±14	15-72
Albumin (g dL^{-1})	3.80±0.7	2.4-4.9
Hemoglobin (g dL^{-1})	12.10±1.6	8.2-14.1
LDH (m dL^{-1})	463.00±238	70-980
ESR	81.00±35	20-140
Selenium	0.33±0.10	0.11-0.49

Table 2: Response evaluation in aggressive NHL studied cases

	No.	(%)
Not assessed	4	10.5
CR (Complete Response)	17	44.7
PR (Partial Response)	9	23.7
SD (Stable Disease)	1	2.6
PD (Progressive Disease)	7	18.4

Patients with aggressive NHL were assessed for response to therapy according to the RECIST criteria, four cases were not assessed; one patient lost follow-up after one cycle and 3 patients did not receive the standard treatment because of poor performance status and or contraindication to curative treatment (Table 2).

As shown in Table 3, there was no significant difference in the mean blood selenium levels between males and females, in both cases (mean 0.33 in males vs. 0.32 in females, p = 0.6) and control (mean 0.82 in males, vs. 0.80 in females, p = 0.4). The mean blood selenium is significantly lower in patients with poorer performance status (0.28 in performance status 2-3 vs. 0.34 in performance status 0-1, p = 0.03). Also the level is significantly lower in patients with stage 3-4 vs. 1-2

Table 3: The relation between blood selenium concentration and different study parameters in NHL cases

Study parameters	Selenium Mean	SD	Significance t	p
Sex				
Male	0.33	0.10	0.42	0.50
Female	0.32	0.10		
Symptoms				
Absent	0.34	0.09	1.10	0.30
Present	0.31	0.11		
Performance status				
0-1	0.34	0.10	2.20	0.03
2-3	0.28	0.10		
Stages				
1, 2	0.37	0.08	2.50	0.02
3, 4	0.30	0.10		
LDH				
Normal	0.34	0.11	0.70	0.40
Elevated	0.31	0.10		
Pathological grade				
Low grade	0.34	0.12	0.10	0.90
Aggressive	0.33	0.09		
Response				
CR	0.36	0.07	1.60	0.10
No CR	0.31	0.10		

Table 4: correlation of blood selenium level concentration with age and hematologic parameters

Parameters	r	p
Age	0.181	0.209
Albumin	0.292	0.040
Hemoglobin	0.057	0.695
LDH	-0.163	0.258
ESR	-0.135	0.350

(mean 0.3 vs. 0.37, p = 0.02). There was a trend for blood selenium level to be lower in patients who did not achieve CR than those who achieved CR, but the difference was not statistically significant (p = 0.1). The presence of B symptoms, elevated blood LDH level, or aggressive pathology did not have significant impact on blood selenium level.

The blood selenium level showed a significant positive correlation with serum albumin, but no significant correlation was found with any other hematological parameters. Also no statistically significant correlation was found between blood selenium level and age neither in patients (r = 0.16, p = 0.2) nor in the control (r = -0.26, p = 0.2) (Table 4).

DISCUSSION

In the present study, lower blood selenium level was found in patients with newly diagnosed non-Hodgkin's lymphoma than control subjects. This finding is consistent with lower serum selenium levels in a variety of cancers (Sanz Alaejos and Diaz Romero, 1993; Li *et al*., 2004) and in lymphoid malignancy (Avanzini *et al*., 1995). Enhanced uptake of selenium by the neoplastic tissue might be responsible for depleting the trace element content of the blood and other tissues, thereby lowering serum selenium concentrations.

The inverse association observed in the present study between the stage of non-Hodgkin's lymphoma and selenium status suggest that advanced stage disease (3, 4) was associated with lower blood concentration of the trace element. This inverse association between progression of non-Hodgkin's lymphoma and selenium status observed in the present study is consistent with previous observations in patients with cancer (Overvad *et al*., 1991; Lajtman *et al*., 1994) and also in patients with lymphoid malignancy (Avanzini *et al*., 1995). The decreasing concentrations of selenium with disease progression might be due to disease-mediated dietary changes, which are more pronounced in patients with advanced disease. This hypothesis, however, was not tested in the present study or in previous investigations. However in our patients and in similar study (Avanzini *et al*., 1995), no association was observed between selenium status and the presence of systemic symptoms, which might also have been linked to changes in dietary habits. A second hypothesis to explain the decreasing levels of selenium in untreated cancer patients with advanced disease arises from the observation that selenium compounds tend to concentrate in neoplastic tissues in a variety of human and animal tumors (Zachara *et al*., 1997; Charalabopoulos *et al*., 2006).

No association was observed in the present study between the grade of non-Hodgkin's lymphoma and selenium status; this contradicts with the results of Avanzini and his colleagues (Avanzini *et al*., 1995), who reported a lower selenium level in high grade than intermediate and low grade lymphoma. However in their study, the WHO classification was not used and the number of patients with high-grade lymphoma (5 cases) was very low and therefore these results must be evaluated with caution, especially since serum levels of selenium were higher in patients with intermediate-grade than in those with low-grade disease.

The mean selenium concentration was significantly higher in patients with good performance status; this agrees with Last *et al*. (2003). This correlation may be the result of general nutritional deficiency in the months and weeks before diagnosis or an acute phase response of selenium to illness (Nichol *et al*., 1998).

A significant positive correlation between selenium levels and albumin was detected in present study; this is in agreement with Avanzini *et al*. (1995). A direct association between albumin and selenium levels might be explained by nutritional factors or by the fact that albumin represents a selenium-containing protein (Deagen *et al*., 1991). A variation in albumin and selenium independently induced by the progression of the

lymphoid neoplasm might also be hypothesized. The current study showed no correlation with any other parameter. In one trial selenium correlated with serum hemoglobin (Avanzini *et al*., 1995).

In a group of 51 patients with cutaneous T-cell lymphoma pretreatment selenium concentration correlated with response to treatment and proved to be independent predictive of outcome in a multivariate analysis that included clinical variables as cofactors (Nichol *et al*., 1998). In a subsequent study, selenium concentration at diagnosis was reported to be independently predictive of both treatment response and long-term survival in patients with aggressive non-Hodgkin's lymphoma (Last *et al*., 2003). In the current study there was a trend for selenium level to be lower in patients with aggressive non-Hodgkin's lymphoma who did not achieve CR than those who achieved CR, but the difference did not attain the level of statistical significance ($p = 0.1$), which may be explained by the small number of patients evaluable for assessment of the response.

In conclusion, the results of the present study in conjunction with other trials suggest that the concentration of selenium in newly diagnosed non-Hodgkin's lymphoma is lower than in normal population. The level also is inversely associated with the clinical stage of the disease and the performance status and may predict for the response to treatment in aggressive lymphoma. These relationships deserve further trials to investigate the chemopreventive prognostic and the possible therapeutic role of selenium in non-Hodgkin's lymphoma and other malignancies.

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