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Serum CA125; as a Diagnostic and Prognostic in Pediatric Lymphomas

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Elevated serum Cancer Associated Antigen 125 (CA125) levels have been reported in non-gynecologic tumors. Some adult studies showed that elevated CA125 levels correlate with advanced disease, poor response to treatment and lower survival rates. To evaluate CA125 levels in patients with Hodgkin's Disease (HD) and Non-Hodgkin's Lymphoma (NHL) and to investigate the correlations between CA125 levels, disease stage, pathology, response to therapy and outcome a 22 pediatric patients (9 with HD and 13 NHL) were prospectively studied. Serum CA125 assessment was done at diagnosis, during treatment and at end of therapy. CT scans of the chest, abdomen and pelvis were done at diagnosis, during and at end of therapy to document response. The correlations between serum CA125 levels and disease stage, pathology, response to therapy (documented by repeat CT scans of the involved sites) and outcome were statistically evaluated. Present results showed that the mean serum CA125 levels were elevated in 63.6% of children with lymphoma. While statistically significant more NHL patients showed abnormally elevated serum CA 125 (76.9% in NHL vs 44.4% in HD) $p = 0.02$, yet there was no significant difference regarding the magnitude of elevation in CA125 levels ($p = 0.3$). Significantly higher mean serum CA 125 levels were observed in patients with advanced stages (stage III, IV) $p = 0.001$. Mean CA 125 level significantly dropped in response to therapy with a mean diagnostic level of (143.45±168.05) compared to end of therapy mean level of (11.47±6.71) with $p = 0.003$. All patients with elevated CA125 at diagnosis who achieved complete remission had normalization of CA 125 by the end of therapy. On the contrary, none of those who failed therapy had a return of serum CA 125 to normal levels ($p = 0.0003$). None of patients who had normal serum CA125 succumbed to their disease compared to 3/14 (21.4%) who had high serum CA125 at diagnosis. As a conclusion we found that Serum CA125 is a useful tumor marker in pediatric patients with lymphomas. A high CA125 level at diagnosis correlates with advanced disease and poor outcome. Repeated CA125 measurements are useful in monitoring response to treatment

Key words: Pediatric lymphoma, CA125, tumor markers, NHL, HL

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INTRODUCTION

Several studies have reported an association of high CA125 serum levels with advanced Non-Hodgkin's Lymphoma (NHL) as well as a relationship between high CA125 values and poor out come. CA125 is a glycoprotein expressed by epithelial ovarian tumors. It is recognized by monoclonal antibody CA125. Its serum level is commonly used to monitor response to therapy in patients with ovarian carcinoma (Bast *et al*., 1983; Canney *et al*., 1984). Increased CA125 levels have also been reported in non-gynecologic tumors. *In vitro* studies have shown that human mesothelial cells secrete CA125 and that its secretion is enhanced by cytokines releasing tumors. Elevated serum CA125 levels have been reported in patients with other malignancies including leukemia and non-Hodgkin's lymphoma, especially those with mediastinal or peritoneal involvement (Fehm *et al*., 1998; Burney *et al*., 1999; Morra, 1999; Camera *et al*., 2000; Bairey *et al*., 2003). CA125 was reported (Dilek *et al*., 2005) to be a reliable biologic marker for the staging and monitoring outcome of patients with NHL in adult patients.

In this prospective study we use serial measurements in conjunction with other markers, for monitoring response to treatment aiming to investigate the value of measuring CA125 at different stage of the disease (NHL and HL) and to follow up the results of treatment in order to identify CA125 as a useful marker for diagnostic and prognostic tool in pediatric lymphoma.

MATERIALS AND METHODS

This was a prospective study conducted between September 2004 and February 2006. Twenty two lymphoma (9 HD and 13 NHL) patients were included in this study, 13 (58.1%) males and 9 (41.9%) females, with a mean age of 8.09±3.38 years and a mean follow up duration of 9±4.1 months. Patients were recruited from Ain Shams University Pediatric Hematology/Oncology Clinic and underwent serum CA 125 assessment at diagnosis, 3 months on therapy and at end of therapy; other prognostic serum markers (ESR, LDH) were also done at the same time. CT scans for objective assessment of the primary sites were done also at the same intervals. Patients were classified according to tumor histology into HD and NHL. Clinical staging was done to all patients at diagnosis based on history (for B symptoms), physical examination, bone marrow aspirate and biopsies, plain chest X-rays and CT chest, abdomen and pelvis. Patients were treated according to Ain Shams Pediatric Oncology Lymphoma protocols. Complete Response (CR) was defined as the disappearance of clinical and radiographic evidence of disease, partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular dimensions of the tumor, No-Response (NR) was defined as <50% decrease in the tumor mass or tumor growth during therapy.

Serum CA125 assay: Blood was collected under sterile technique and serum was separated and stored at -70°C until time of assay. Serum CA125 was measured using CanAg CA125 kit (CanAg Diagnostics AB Sweden). It is a solid phase, non-competitive immunoassay based upon the direct sandwich technique. A serum level of 30.1 μ mL^{-1} (mean+2 SD) was used as a Cutoff value based on the company's (CanAg Diagnostics AB Sweden) published data for normal serum CA125 values.

Statistical analysis: Was done using SPSS version 10 for windows. Tests used included, Chi-square and Fisher's exact test. Kaplan-Meier test for survival analysis and Log Rank test for comparison of survival. For all tests, p-value <0.05 was considered significant.

RESULTS

Twenty two patients were included in this study. Their main clinical, pathologic characteristics are presented in (Table 1).

Serum biological markers at diagnosis: Serum CA125 was elevated above cut-off value (30.1 μ mL^{-1}) in 63.6% (14/22) of patients. The mean value of elevated serum CA125 dropped from 143.45±168.05 U mL^{-1} at diagnosis, to 71.75±138.72 during therapy and 11.47±6.71 at the end of therapy (Table 2).

Relation between serum CA125 and type of lymphoma: 76.9% (10/13) of NHL patients had elevated serum CA125 while only 44.4% (4/9) of HD had high serum CA125 P=0.02. Patients with HD had lower mean CA125 at diagnosis (98.67±133.03) compared to NHL (174.46±187.29), yet it did not reach statistical significance (p = 0.31).

Magnitude of mean serum CA125 elevation and disease stage: There was a statistically significant higher mean serum level of CA125 in high stage (III, IV) patients with a mean serum CA125 of 187.50±178.07 compared to 26±26.93 in stage II patients (p = 0.001). While ESR was significantly higher in advanced stage disease (p = 0.01); yet LDH elevation did not reach statistical significance p = 0.09 (Table 3).

Table 1: Clinical and pathological characteristics of lymphoma patients

Characteristics	No.	Percentage
Gender		
Male	13	59.1
Female	9	40.9
Clinical findings		
B Symptoms	10	45.5
Hepatomegaly	8	36.4
Spleenomegaly	13	59.1
Extranodal involvement	10	45.5
Stage		
II	6	27.3
III	12	54.5
IV	4	18.2

Table 2: Laboratory results of the whole lymphoma group

Laboratory results	Mean±SD
WBC	6.97±3.29
HGB	9.32±1.51
PLT	325.18±180.77
ESR	51.86±36.53
LDH	1012.09±779.88
ALT	30.55±19.01
TBILI	0.90±0.68
Diagnostic Serum CA125 level	143.45±168.05
On therapy serum CA125 level	71.75±138.72
End of therapy serum CA125 level	11.47±6.71

Table 3: Comparison between mean levels of different serum markers in lymphoma based on disease stage

	Disease stages		
Serum markers	Low stage (6)	High stage (16)	p
LDH	555.50±297.18	1183.31±841.07	0.090
ESR	20.67±12.0	63.56±35.8	0.010
CA125	26.00±26.93	187.50±178.07	0.001

A statistically significant higher ESR and CA125 was seen in advanced stages of lymphoma

Impact of therapy on CA125 level: Mean serum CA125 level dropped significantly in response to therapy in both HD and NHL patients [mean diagnostic level was 143.45±168.05 while end of therapy level was 11.47±6.71] p = 0.001 (Fig. 1).

Correlation between serum CA125 and other disease (lymphoma) markers: There was a significant positive correlation between serum CA 125 and ESR (R = 0.52, p = 0.02),. No significant correlation was found between CA125 and serum LDH (p = 0.25).

Remission status and survival among HD and NHL patients: More patients went into remission earlier in HD (CR in HD after 4 cycles was 88.9% compared to 50% in NHL) yet at end of therapy both achieved comparable remission rate 77.8% in HD and 80% in NHL. Patients with HD showed higher survival rates (100%) compared to NHL (76%), yet the difference did not reach statistical significance p = 0.12 (Fig. 2).

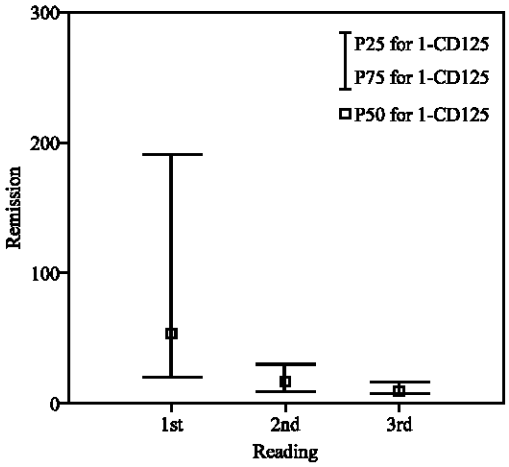

Fig. 1: Mean serum level of CA125 interquartile range compring diagnostic ample (1st) to follow up samples (2nd, 3rd) in patients who went into remission: showing highly significant drop in the on therapy sample (2nd) as well as end of therapy sample (3rd) (p = 0.003)

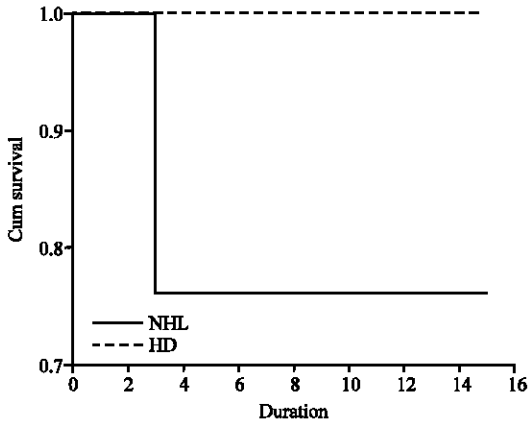

Fig. 2: Kaplan-Meier survival curve in HD and NHL: The probability of survival after one year in HD: 100 and 76% in NHL Yet the difference did not reach statistical significant (Log Rank test) p = 0.12

Serum CA125 as a predictor of response to therapy: Serial CA125 measurements showed that all patients with elevated CA125 at diagnosis who achieved complete remission (11 patients) had normalization of CA125 by the end of the treatment. On the contrary, none of those who failed therapy (3 patients) had a return of their serum CA125 to normal levels p = 0.0003 (Fig. 3).

Serum CA125 as a predictor of survival: None of patients (0/8) who had normal serum CA125 at diagnosis succumbed to their disease compared 21.4% mortality (3/14) in those who had high levels p = 0.002.

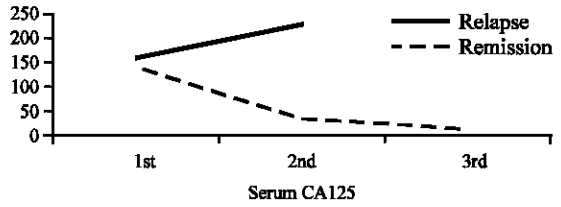

Fig. 3: Graphic presentation of diagnostic and follow up samples of CA125 in patients who went into remission compared to patients who did not/or who showed initial remission followed by relapse $p \leq 0.0003$

DISCUSSION

A variety of pretreatment clinical characteristics have been identified to be associated with response to treatment and survival of patients with NHL (Anonymous, 1993). CA125 is widely used as a tumor marker in the monitoring of epithelial ovarian cancer. Serum CA125 level has also been reported to be a significant prognostic factor for complete remission and survival in patients with NHL (Benboubker *et al*., 2000). High serum CA125 levels in NHL patients correlated with advanced disease, mediastinal and/or abdominal involvement, bulky tumors, high tumor burden, effusions, extragonadal extension, LDH activity and elevated B2 microglobulin (Benboubker *et al*., 2000; Lazzarino *et al*., 1998). The peritoneal mesothelial cells stimulated by the lymphokines produced by lymphoma cells have been suggested to be responsible for the high serum levels of CA125. Apel and Fernandes (1995), Pabst and Ludwig (1995) CA125 was reported (Dilek *et al*., 2005) to be a reliable biologic marker for the staging and monitoring outcome of patients with NHL in adult patients. In the present study, serum CA125 levels were elevated in 63.6% of pediatric patients with lymphoma, confirming the adult and pediatric findings of elevated serum CA125 as a biological marker for lymphoma (Zidan *et al*., 2004; Birgen *et al*., 2005).

Serum CA125 elevation was observed more frequently and to higher levels among patients with NHL compared to Hodgkin's disease. This finding is consistent with the more aggressive nature of NHL as well as its tendency to affect the abdomen and involves the peritoneal surfaces, which secretes more CA125. Advanced stage disease (stage III and IV) showed higher levels of serum CA125 levels compared to lower stages (stage II). These finding is consistent with the adult and pediatric literature showing the association between high CA125 levels and advanced disease (Kutluk *et al*., 1999; Ozguroglu *et al*., 1999; Dilek *et al*., 2005; Wei *et al*., 2006).

In the adult population (Lazzarino *et al*., 1998), there were higher CA125 levels in aggressive NHL than in low-grade NHL.

The present study showed higher response to therapy as well as survival rates in patients with normal CA125 levels than in those with high levels at diagnosis, non of the patients with normal CA125 at diagnosis failed therapy and all of them were alive at the end of therapy while 21.4% of patients with high serum CA125 at diagnosis succumbed to their disease. This finding is in concordance with published data showing that serum CA125 level is an indicator of response to therapy and survival in NHL patients (Zacharos *et al*., 2002; Zidan *et al*., 2004; Batlle *et al*., 2005) where Bonnet and his colleges 2007 (Bonnet *et al*., 2007) stated that serum CA125 level correlates significantly with a number of features associated with more aggressive disease, it does not enhance the performance of standard prognostic markers in the management of patients with NHL or HL.In addition, high CA125 levels were associated with clinical features of aggressive and advanced stage disease.

Serial measurements of serum CA125 during and at the end of treatment showed strong relationship between dropping of CA125 level and response to therapy. All patients with high CA125 levels at diagnosis had normalizations of this marker when they achieved complete remission. On the other hand, CA125 levels remained high in patients who did not go into remission. Similarly other researchers (Zidan *et al*., 2004; Birgen *et al*., 2005) reported normalization of serum CA125 in patients who subsequently went into remission.

CONCLUSION

Serum CA125 is a useful tumor marker in pediatric patients with lymphoma. A high CA125 level at diagnosis correlates with advanced disease and poor outcome. Repeated CA125 measurements are useful in monitoring response to treatment and in the follow-up for early detection of relapse.

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