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ORIGINAL ARTICLE

Prognostic Value of Accumulative Expression of COX-2 and p53 in Small and Diffuse Large B Cell Lymphoma

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Abstract

Cyclooxygenase-2 (COX-2) plays an important role in carcinogenesis, which catalyzes the conversion of arachidonic acid into prostaglandins. P53 is a tumor suppressor gene that contributes to apoptosis and cell cycle control. There is functional interaction between p53 and COX-2, which lead to abrogation of apoptosis and progression of malignancy. To assess the relationship between COX-2, p53 expression and the clinicopathololgic features in SLL and DLBCL. We immunohistochemically examined the expression of COX-2 and p53 in non-neoplastic lymphoid cells, lymph nodal low-grade (50 cases of SLL), intermediate and high-grade lymphomas (100 cases of DLBCL) and their corresponding bone marrow specimens. The expression of COX-2 and p53 was absent in the in non-neoplastic lymphoid cells. In contrast, their expression values increased progressively with the advancing grade of lymphoma ($p < 0.001$). COX-2 expression was significantly associated with advanced disease stage, high-grade lymphomas, and disease relapse and p53 expression. The p53was detected in 64.5% in patients positive for COX-2. The expressions of COX-2 and p53 proteins, were significantly associated with shorter overall-survival and progression free survival. Here we report up-regulation of COX-2and p53 protein expression in SLL and DLBCL indicating their interactive involvement in the pathogenesis of lymphoma. Our data provide a rationale for further investigation of COX-2 expression in lymphomas for potential prognostic, chemopreventive and chemotherapeutic purposes.

Keywords p53 · COX-2 · Lymphoma

Introduction

Non Hodgkin lymphoma has different groups of clinic-pathologic types as a result of malignant transformation of lymphocyte into low grade or high grade lymphoma. Low grade lymphoma as small lymphocytic lymphoma (SLL) is an indolent neoplasm, that often occurs in elderly usually involvement bone marrow with satisfactory response to chemotherapy but cure is rarely achieved [1–6]. High grade lymphoma is rapidly growing aggressive neoplasm as diffuse large B cell lymphoma (DLBCL) that usually arising de novo, but it can supervene from a small lymphoma or via chronic inflammation [6–12].

COX-2 is a pro-inflammatory enzyme normally not expressed in tissues that mediates several inflammation processes [13]. The contribution of COX-2 to carcinogenesis thought to be related to its abilities: (1) increase production of prostaglandins;(2) convert procarcinogens to carcinogens; (3) inhibit apoptosis; (4) promote angiogenesis; (5) modulate inflammation and immune function [14–17]. Overexpression of COX-2 is reported in several malignancies as colon, esophagus, stomach, and a variant type of Non-Hodgkin lymphoma, and Hodgkin lymphoma [14–22]. COX-2 expression in lymphomas is related to enhancement of proliferation, angiogenesis and tumor invasion [17, 23, 24]. The expression of COX-2 in the carcinogenesis process suggests that selective

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inhibitors of COX-2 may have promising therapeutic role in lymphomas [25, 26].

The p53 tumor suppressor protein is a critical mediator of apoptosis and carcinogenesis [27–29], overexpression of p53 is common in many types of lymphomas [19, 30] There are functional interactions between p53 (a tumor suppressor) and COX-2 (a mediator in carcinogenesis). The p53-dependent COX-2 upregulation is an important pathway by which p53 can abrogate its effect in apoptosis and growth inhibition [31]. So, we hypothesize that "the expressions of COX-2 pro-inflammatory enzyme and p53 tumor suppressor protein are altered as histological grade of lymphoma.

The pattern of expression of both COX-2 and p53 in SLL and DLBCL (in the lymph node and bone marrow) remains unknown. Our goals included: i) evaluation incidence and relation of the COX-2 and p53 expression to SLL and DLBCL, ii) assessment of prognostic roles of COX-2 and p53. To achieve our goals, we used immunohistochemical staining methods to examine COX-2 and p53 protein expression in of SLL and of DLBCL (lymph nodes and bone marrow).

Patients and Methods

Patients The study included 150 cases with NHL (50 cases of SLL and 100 cases of DLBCL) from the medical oncology department in South Egypt Cancer Institute, Assuit University. The ethics committee and Review Board of South Egypt Cancer Institute approved study design and informed consent before commencing on the research from all participants. Biopsies of the lymph nodes and bone marrow were obtained from the archival material of Pathology and Clinical Pathology Laboratories, the specimens represent the disease condition before treatment. Full clinicopathololgic features were recorded.

Immunohistochemistry The presence of COX-2 and p53 proteins was examined using Avidin-biotin immunoperoxidase complex (13–15). Briefly, 4-μm thick tissue sections (lymph nodes and bone marrow) collected on glass slides, then deparaffinizion and rehydration in graded ethanol solution after antigen retretrieval in EDTA/ Tris buffer (pH 7.3) by heating for 12 min (lymph node biopsies) and 6 min (bone marrow biopsies). Endogenous peroxides were blocked with 20% of H_2O_2 by 5 min for three cycles, then blocking of nonspecific binding protein by exposure to 10% normal goat serum for 10 min. Then incubated with rabbit polyclonal antibody raised against COX-2 (at the dilution of 1:200 dilution, Thermo scientific, Lab Vision Corporation, Fremont, CA94538–6406, RB-9072-P1, USA) and with rabbit polyclonal antibody raised against p53 (at a dilution of 1:200 dilution, Thermo scientific, Lab Vision Corporation, Fremont, Clone SP5, RM-9105-S1, USA) for 30 min at room temperature. A detection system used following the instructions of the manufacturer (Catalog number CA 94539 Ultravision plus detection system antipolyvalent HRP/DAB, ready to use, Thermo-scientific Corporation Fremont, CA, USA). Sections were incubated with 14-diaminobenzidine and 0.06% H_2O_2 for 5 min, then were dehydrated and stained by H&E stain. Evaluation of the slides done by three observers *(Dr M. Rezk, DR. D. elsers, DR. R. Bakry)*.

Positive Control Sections from colonic adenocarcinoma considered as positive control for COX-2 and p53. The positivity for COX-2 was identified as brownish cytoplasm and membrane staining of tumor cells. The positivity for p53 was identified as brownish nuclear staining of tumor cells Fig. 1 and 2.

Negative Control Tissue-specific negative controls of normal colon tissue for COX-2 and p53, respectively. In parallel, additional sections were stained without the primary antibodies.

Evaluation of COX-2 and p53 Staining Immunohistochemical evaluation of COX-2 and p53 was performed following other groups [13, 32]. The positive and negative controls were positive and negative, respectively indicating the validity of our results. The immunohistochemical staining was scored in a semiquantitative fashion, incorporating both the intensity and distribution of specific staining. Briefly, the evaluation was recorded as percentages of positively stained target cells in each of five rated intensity categories (from 0: no staining, to 4: very strong staining). For each section, a value designated the H-score was derived by multiplying the percentages of cells staining and intensity of staining. The values of H-scores ranged from 0 to 400.

Statistical Analysis Fisher test was used to compare statistical differences between groups and considered significance in P value less than <0.05. For survival study The Kaplan–Meier method and compared with the log-rank test and analyzed by Multivariate Cox hazard test using SPSS version software 6.2 (SAS Institute, Cary, NC, USA). Progression-free survival (PFS) calculated from time to initiation of the treatment to time of relapse and censored non-lymphoma-related deaths. Overall survival (OS) calculated from beginning of the treatment until death or the last follow-up.

Results

Clinicopathologic Features of SLL and DLBCL A summary of the parameters including age, sex, stage of disease, B symptoms, performance state, pathology, response to

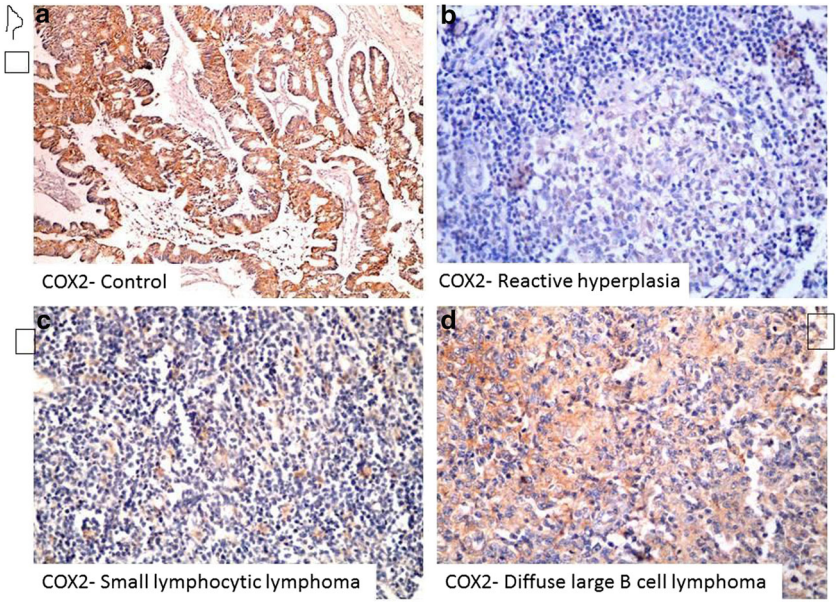

Fig. 1 COX-2 protein expression in the control (**a**: colonic adenocarcinoma), reactive hyperplasia (**b**: absent to faint reactivity), small lymphocytic lymphoma (**c**: weak expression) and diffuse large B cell lymphoma (**d**: strong diffuse expression). (original magnification 400×)

chemotherapy, relapse and p53 expression in relation COX-2 positive cases are demonstrated in (Table 1). A significant association of COX-2 expression in relation to histological type of NHL (*p* value 0.0001) and associated with high relapse rate (p value 0.001). Analysis of clinical parameter to expression of p53 was analyzed in (Table 2).

The Values of Expression COX-2and p53 Proteins in Bone Marrow Biopsies and Lymph Node Significantly Increased with Advance of Histological Grade of Lymphoma COX-2 expression was observed in 19 and 74 cases on SLL and DLBCL, respectively. A positive nuclear p53 protein expression observed in 60 patients also positive in COX-2 (20 SLL and 40 DLBCL, respectively) with a significant correlation between COX-2 and p53 expression ($P = 0.0007$) Table 1.

COX-2 and p53 immunoreactivity H scores significantly upregulated in DLBCL in comparison to SLL in both lymph node and bone marrow ($P = 0.0001$) (Table 3).

The Correlation Between Expression COX-2and p53 and Survival Patients showed both combined expression for both COX-2 and p53 showed worse significant survival in PFS and

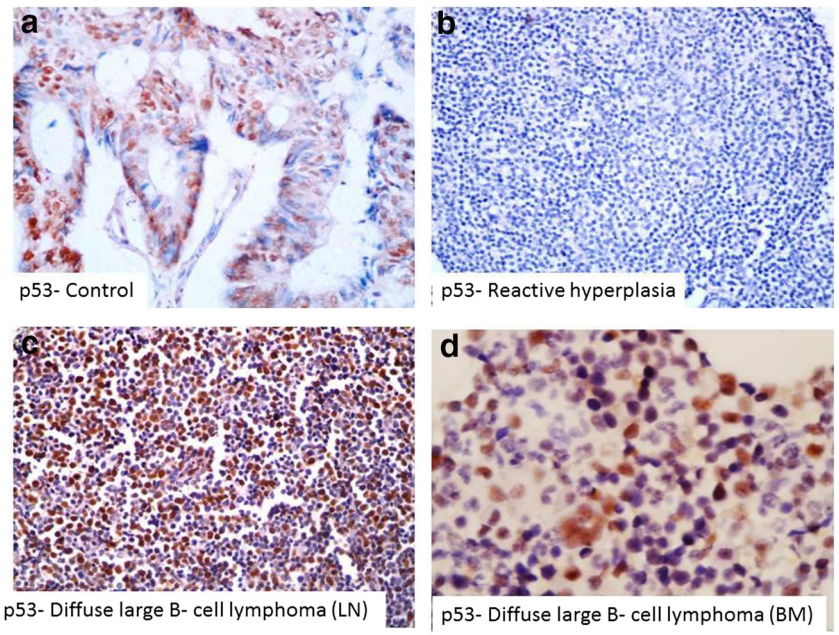

Fig. 2 p53 protein expression in the control (**a**: colonic adenocarcinoma), reactive hyperplasia (**b**: absent expression), diffuse large B cell lymphoma of the lymph nodes and bone marrow (**c** and **d**, respectively: strong diffuse expression). (original magnification 400×)

Table 1 Clinical parameters of patients according to COX-2 Expression

Parameter	COX2 positive cases (*N* 93)	Cox2 negative cases (*N* 57)	*P* Value
Age	55.24 ± 15.3	57 ± 16.74	0.32
Sex (M/F)	50/43	30/27	0.74
Stage (early/advanced)	40/53	29/28	0.4
B symptoms (present /absent)	47/46	29/28	0.978
Performance state (good/poor)	73/20	43/14	0.69
SLLDLBCL	19/50	31/50	0.0001*
	74/100	26/100	
Response to CT (present /absent)	13/80	8/49	0.992
Relapse (present /absent)	53/40	17/40	0.001*
P53 Expression	60/93	20/57	0,0007*

OS (Log rank *P* value 0.002 and 0.001 respectively) as shown in (Fig. 3). By using multivariate analysis (Multivariate Cox Hazard Regression test) showed significant effect of expression of COX2 expression in survival of patients in regard to a pathological entity as obvious in Tables 3 and 4 as risk of worsen the prognostic effect (Tables 4 and 5).

Discussion

The chronic inflammation is accompanied by persistent immune stimulation that eventually lead to proliferation of B-lymphocytes and malignant transformation [33]. Several experimental support this notion. DLBCL associated with chronic inflammation is recognized, as pyothorax accompanied lymphoma [34, 35], Helicobacter-pylori-associated gastric lymphoma [36] and rheumatoid arthritis associated with non-Hodgkin's lymphoma [37]. Clinically, it is characterized by a poor prognosis [34, 38]. Several studies indicated that COX-2 inhibitor drugs can prevent carcinogenesis [20, 39–41].

In this investigation, we hypothesized that "the expressions of COX-2 pro-inflammatory enzyme and p53 tumor suppressor protein are altered with histological grade of lymphoma advances". Our result provides the first indication about the pattern of expression COX-2 and p53 in SLL and DLBCL on both lymph node and bone marrow. Our study revealed three observations: i) expression value of COX-2 and p53 proteins significantly increased in lymph nodes and bone marrow with the advances the histological grade of lymphoma (i.e. low expression in SLL versus high expression values in DLBCL), ii) significant correlation between COX-2 and p53 expression and poor survival rate in lymphoma patients.

The Expression Values of COX-2 and p53 Proteins in the Lymph Nodes and Bone Marrow Significantly Increasing with Advances of the Histological Grade of Lymphoma Here we firstly report of overexpression of COX-2 and p53 proteins in the nodal and bone marrow, which significantly higher in DLBCL than SLL, Our findings suggest overexpression of COX-2 and p53 may represent an interesting molecular pathway that contribute to lymphomagenesis. Our findings are consistent with previous investigations in NHL [24, 25,

Table 2 Clinical parameters of patients according to p53 Expression

Parameter	p53 positive cases (*N* 80)	p53 negative cases (*N* 70)	*P* Value
Age	55.24 ± 15.3	57 ± 16.74	0.32
Sex (M/F)	40/40	30/40	0.41
Stage (early/advanced)	34/46	31/39	0.87
B symptoms (present /absent)	57/23	42/28	0.169
Performance state (good/poor)	52/28	39/31	0.315
Type (SLL/DLBCL)	19/61	31/39	0.009*
Response to CT (present /absent)	23/57	18/52	0.716
Relapse (present /absent)	53/27	27/43	0.0009*

Table 3 Correlation of expression (H score) in LN and BM biopsy by immunohistochmistry for Cox2 and P53 and pathological type of NHL

Aspects	SLL (LN)	DLBCL (LN)	*P* value	SLL (BMB)	DLBCL (BMB)	*P* value
COX-2	16.4 ± 7.2	200,1 ± 20.4	***P* < 0.001**	28.8 ± 9.8	100.7 ± 30	***P* < 0.001**
p53	7.9 ± 4.1	100.9 ± 20.8	***P* < 0.001**	2.5 ± 1.7	100.8 ± 20.8	***P* < 0.001**

Signficance accumulation of COX-2 and p53 from low grade to high grade lymphoma in both Lymph node and Bone marrow staining are in bold

30, 42]. Wun et al., demonstrated an increase in COX-2 protein expression approximately about 3 fold in B lymphoma cell lines. Treatment with a COX-2 inhibitor was dose-dependent lead to decreased proliferation and initiation of apoptosis in lymphoma cell lines. The authors indicated that COX-2 expression contribute to lymphomagenesis. They proposed that inhibition of COX-2 had a promising role in the lymphoma treatment [25]. A carcinogenic role of COX-2 overexpression is increasing the synthesis of prostaglandins; conversion of procarcinogens to carcinogens; inhibition of programmed cell death, and promotion of cell invasion [43–50]. ,COX-2 enhances expression of both proangiogenic and angiogenic factors like PGE2, Which promote tumor angiogenesis [51].

Li, et al. studied the expression of p53 protein expression in gastric MALT lymphoma. The nuclear expression of P53 was shown in 19/32 patients (11 of 23 in low-grade type and in 8 of 9 of high-grade). The expression of p53 significantly accumulated between low grade and high-grade cases and accumulation of staining correlated with advanced clinical stage [30]. In our study, p53 positively significantly increased as advanced the histological grade, which supports the concept of transformation in lymphoma disease associated with the expression of p53. The carcinogenic roles of p53 are related to its role in cell-cycle control, maintenance of DNA stability, cell differentiation and apoptosis. Mutations of the p53 gene lead to nuclear accumulation of a mutant p53 protein with extended half time [27–29].

The Correlation Between COX-2 and p53 We found a significant correlation between COX-2 and p53 in SLL and DLBCL, which previously reported in some solid malignancies such as ovarian adenocarcinoma, head and neck tumors [52, 53]. Using an expression array analysis, Han and his colleagues reported that COX-2 expression is induced by mutation of p53 and DNA damage. This p53-induced COX-2 expression results from p53-mediated activation of the Ras/Raf/MAPK cascade, counteracting p53-mediated apoptosis. In support, p53-induced apoptosis was enhanced greatly in COX-2 knock-out cells as compared with mutant-type cells, suggesting the abrogation effect of COX-2 on p53-induced apoptosis [53]. Subbaramaiah et al., compared the COX-2 expression between the wild type p53, mutant p53 and p53 non-expressing mouse fibroblasts. COX-2 expression was markedly repressed by mutant p53. The authors proposed that this finding may explain why these levels of COX-2 protein are not seen in normal epithelial cells and contrarily why mutant p53 increases the levels of COX-2 in malignant tissues [54–56].

The Correlation Between COX-2 Expression and Survival The expression of COX-2 and p53 proteins correlated significantly with poor survival, which consistent with previous reports [24, 42]. Hazar, et al. reported poor and short survival in lymphoma patients and poor response to chemotherapy, which indicated the prognostic role of COX-2 in lymphoma. These suggest combining COX-2 inhibitors with standard chemotherapeutic could be a potential

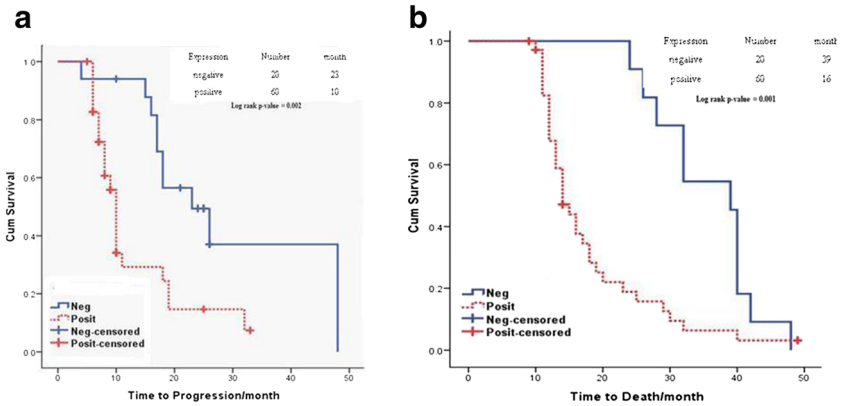

Fig. 3 survival curves of patients show combined positive expression for both COX-2 and p53 proteins (**a**, for progression free survival and **b** for over all survival)

Table 4 Multivariate Cox Hazard Regression of the OS associated Correlates

	P value	HR*	95.0% CI**	
			Lower	Upper
COX-2 expression				
• Negative	1 (Reference)			
• Positive	**0.002**	**3.057**	**1.486**	**6.287**
Type				
• DLBCL	1 (Reference)			
• SLL	0.494	1.417	0.521	3.850
Stage				
• Early	1 (Reference)			
• Advanced	0.540	1.449	0.443	4.738

Signifcant association between COX-2 expression and Overall survival are in bold

*HR = Hazard Ratio

**CI=Confidence Interval

treatment options in lymphomas [42, 57]. Khalifeh et al. examined the expression of COX-2 and p53 was compared between the primary peritoneal serous carcinoma and in ovarian carcinoma, which found high expression associated with worse survival rate in primary ovarian serous carcinoma cases [57, 58].

To conclude, our study provides the first indication about the expression of COX-2 and p53 in the SLL and DLBCL (lymph nodes and bone marrows). The overexpression of COX-2 is a negative prognostic parameter. Our data provide a rationale for further investigation of COX-2 expression in lymphomas for potential prognostic, chemoprevention and chemotherapeutic purposes.

Table 5 Multivariate Cox Hazard Regression of the PFS associated Correlates

	P value	HR*	95.0% CI**	
			Lower	Upper
COX-2 expression				
• Negative	1 (Reference)			
• Positive	**0.004**	**3.121**	**1.439**	**6.770**
Type				
• DLBCL	1 (Reference)			
• SLL	0.146	1.802	0.814	3.990
Stage				
• Early	1 (Reference)			
• Advanced	0.280	1.708	0.647	4.512

Signifcant association between COX-2 expression and progression free survival are in bold

*HR = Hazard Ratio

**CI=Confidence Interval

Compliance with Ethical Standards

Conflict of Interest No conflict of interest.

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