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Status of NGAL in Lung Cancer

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Abstract—*Lung carcinoma is the major cause of premature and avoidable mortality worldwide. According to the American Cancer Association statistics, the overall cure rate for lung cancer has not improved significantly over the past times. So, there is a great need of novel factors for early detection of lung cancer to reduce the mortality and morbidity. Meanwhile, a role of Neutrophil Gelatinase Associated Lipocalin (NGAL) has been recognized in lung cancer. The present study proves that NGAL levels were significantly higher in the patients of lung cancer compared to the healthy controls and also there was a decrease in level of serum NGAL in patients after four weeks of treatment. So NGAL may be considered as a potential biomarker for lung carcinoma.*

1. INTRODUCTION

In India, lung cancer has constituted 6.9 per cent of all new cancer cases and 9.3 percent of all cancer related deaths in both sexes). [1] The incidence and pattern of lung cancer differs as per geographic region and ethnicity and largely reflects the prevalence and pattern of smoking. The overall 5-year survival rate is approximately 15 percent in developed countries and 5 percent in developing countries. However, screening by low dose computed tomography (CT) in high risk population demonstrated a relative risk reduction of 20 percent in lung cancer mortality but with a false positive rate of 96 percent.[2] In India where tuberculosis is prevalent, the applicability of such screening tool is questionable.[3] Development of newer non-invasive methods/ biomarkers for early diagnosis and screening of high risk population is warranted.

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths. The International Agency for Research on Cancer (IARC) lists several agents known to cause lung cancer, including arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.[4] The risk for lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking i.e. pack-years of smoking history. Majority of the patients in the present study were bidi smokers, which poses a six times higher risk of lung cancer as compared to cigarette.[5] The incidence of lung cancer increases with larger amount of bidis smoked per day, increased duration of smoking and age to start smoking bidi. [6] Lung cancers are generally divided into 2 main categories: Small Cell Carcinoma and Non-Small Cell Carcinoma. Non-Small Cell Lung Carcinoma accounts for approximately 85% of all lung cancers. [7,8]

Inspite of a variety of diagnostic methods [9], the patients of lung carcinoma remain undetected until a later stage. Therefore, this disease is in great need of novel biomakers for early detection and timely intervention. This quest has led to studying the association of Neutrophil Gelatinase Associated Lipocalin (NGAL) with lung cancer.

NGAL, also known as lipocalin -2 (LCN-2), is a member of lipocalin protein family and is encoded by LCN-2 gene on chromosome 9. The structure and function of LCN-2, described by Flower et al in 1996, comprises of a single eight stranded continuously hydrogen bonded antiparallel beta barrel delineating alpha calyx shape.[10] NGAL binds to specific cell surface receptors and forms macromolecular complexes.[10] NGAL is strongly expressed in several normal adult human tissues including the non-neoplastic breast ducts, kidney, liver, lungs, trachea, small intestine, bone marrow, thymus, prostate, adipose tissue and macrophages. However, it is completely absent in the normal brain tissue, heart, skeletal muscle, spleen, testes, ovary and colon.[11]

NGAL can have both pro-oncogenic and anti-oncogenic activities. The pro-oncogenic activity can be due to its being negative regulator of Red Blood Cell production. NGAL is abundantly expressed in erythroid progenitor cells. During acute anaemia, the expression of NGAL gets reduced by feedback system; which is necessary for the efficient recovery of RBC counts. Many malignancies may partly be due to the abundant secretion of NGAL in tumor cells.[12] The antioncogenic activities correlate to its ability to inhibit the proneoplastic factors. It deprives the bacteria of the growth essential iron, thus, is bacteriostatic.[13]

At present only a few studies are available in literature regarding the role of NGAL in lung cancer. Therefore, this study was planned to evaluate the role of NGAL as a biomarker for early detection and timely management of lung cancer patients.

2. MATERIAL AND METHODS

The study was conducted in the Department of Biochemistry in collaboration with Department of Radiotherapy, Pt B D Sharma Post Graduate Institute of Medical Sciences, Rohtak. For the study, 25 newly histopathologically proven patients with lung carcinoma and 25 age and sex matched healthy individuals were enrolled. Diagnosis was established with help of detailed history, clinical examination, radiological and histopathological examination. Staging was done according to American Joint Committee on Cancer 2014 criteria. [15] Patients of lung carcinoma were treated with the standard dose of radical external radiations (60Gy/ 30 fractions/ 6 weeks). Concomitant Cisplatin (100 mg/m^2 3 weekly/ 3 cycles) was also administered to these patients.

All the subjects were divided into 3 groups.

Group I : Healthy controls (number=25)

Group IIa: Histopathologically proven patients of lung carcinoma before treatment (number=25)

Group IIb: Patients of lung carcinoma carcinoma 4 weeks after completion of treatment (number =25)

2.1 Exclusion Criteria

- Patients medically fit for radical surgery.
- Patients with history of any other chronic disease except cancer.
- Patients already on any other drug supplements/ therapy.

2.2 Methodology

Six mL of venous blood sample was collected in a plain vacutainer under all aseptic precautions from all the patients at the time of diagnosis and 4 weeks after completion of treatment. Similar samples were collected from healthy controls also. Blood samples were processed within one hour of collection. Serum was separated by centrifugation at 2000 rpm X 10 minutes after clotting. Sample was stored at -200C in separate aliquots for estimation of NGAL in batches subsequently. NGAL was estimated by ELISA technique. The data was analyzed using appropriate statistical analysis.

3. RESULTS

In the present study, group I had sex ratio of 20:5(M:F) and group II had 21:4(M:F). The mean age of persons in group I was 47 years while in group II it was 60.2 years. Out of 25 patients from group II, 19 presented with stage III of lung cancer and the remaining 6 presented with stage IV cancer. The levels of NGAL in different groups are shown in table 1.

Table 1: Results

	Control (n=25)	**Cases II (n=25)**	**Cases IIb (n=25)**	**p value between Group I & IIa**	**p value between Group I & IIb**	**p value Group IIa & IIb**
Mean ± S.D	3.43±3.67	4.95±4.25	3.42±2.92	0.0000012	0.11	0.0014

4. DISCUSSION

On the basis of the results, it was proved that the levels of NGAL were raised in the patients of lung cancer as compared to those after treatment and with those of healthy controls. This is much in concordance with the study which proved that NGAL levels were significantly higher in the majority of solid tumors compared to the relative normal tissues for every data analyzed. Great differences were seen in the results of NGAL values between cases and controls. All metastatic tumors showed a decrease of NGAL expression when compared to matched primary lesions.[16] The expression of NGAL is significantly increased in several solid and hematological tumors and has been shown to correlate with both tumor characteristics and disease outcome. NGAL is significantly up regulated in breast, lung, gastric, colon, ovary and pancreatic carcinomas.[14] The concordance of NGAL at both mRNA and protein levels were observed for six cancer types including bladder, liver, colorectal, lung, ovarian and pancreatic carcinoma. NGAL transcript levels were significantly higher in the majority of solid tumors compared to the normal tissues. Friedl et al found high NGAL levels in adenocarcinoma of lung.[16] In contrast, the levels of NGAL were not overexpressed in carcinoid lung cancer. Similarly, in the mouse xenograft model of human lung adenocarcinoma, downregulation of NGAL was demonstrated to reduce tumor growth. Depletion of NGAL expression decreased the ability of cell proliferation and induced cell apoptosis. Furthermore with the addition of N-acetyl cysteine, a scavanger of ROS, it was found that NGAL depletion was sufficient to cause apoptosis of lung adenocarcinoma cells by generating ROS through the inhibition of nuclear factor E-2, heme oxygenase-1 antioxidant pathway.[16]

It may be concluded that NGAL is a candidate marker for tumor growth in lung cancer. Further supporting studies with larger sample size are required to elucidate the function of NGAL in tumor development and metastatic processes.

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