



Alteration of Serum Albumin Globulin Ratio in Patients with Lung Cancer

Authors

Raseela Karunakaran¹, Mithun Harold Thomas², Athul Santhosh³,
Meera Madhusudan⁴

¹Department of Respiratory Medicine, Government TD Medical College, Alappuzha, Kerala, India

²Department of General Medicine, Government Medical College, Kozhikode, Kerala, India

Corresponding Author

Mithun Harold Thomas

Senior Resident, Department of General Medicine, Government Medical College, Kozhikode, Kerala, India

Phone number: 9809587773, Email: drmithunharold@gmail.com

Abstract

Introduction: Recent studies have demonstrated that hypoalbuminemia and low albumin globulin ratio are important predictors of long term mortality in several cancers. To the best of our knowledge, studies on albumin globulin ratio in lung cancer patients has not been carried out in our population.

Aim: To study the alteration in serum albumin, globulin and albumin globulin ratio in patients with histologically diagnosed lung cancer.

Materials and methods: This was a retrospective analysis conducted in the department of pulmonary medicine in a tertiary care centre in Kerala. The case records of 21 patients histologically diagnosed as lung cancer were analysed. Blood samples were collected for testing of total protein and albumin before starting treatment. Patients with comorbidities that could alter albumin globulin ratio such as chronic liver disease, renal disease and other chronic inflammatory diseases were excluded from the study. Albumin-globulin ratio (AGR) was calculated using the equation $AGR = \frac{\text{Total protein} - \text{albumin}}{\text{albumin}}$.

Results: The total number of patients included in the study was 21. The most common histopathological type of lung cancer observed in the study was adenocarcinoma (14/21). Other types were squamous cell (3), small cell (1), carcinoid tumor (1) and poorly differentiated cancer (2). Albumin globulin ratio was < 1 in 14 patients. In another 3 patients the ratio was 1.03. Serum globulin was elevated (> 3.5) in nine patients. Serum albumin was low (< 3.5) in fourteen patients. Total protein was increased above normal (> 7) in two patients in whom globulin was very high (> 5).

Conclusion: Cancer related inflammation has been a subject of interest in the field of cancer research. This study supports the recently changed concept that cancer cells are capable of producing immunoglobulins as against the older concept that immunoglobulins are produced by B cells alone.

Keywords: Lung cancer, Immunoglobulin, Albumin, Globulin.

Introduction

Lung cancer is one of the leading causes of cancer related mortality worldwide⁽¹⁾. Based on the clinical behavior and pathological features, lung cancer is

grouped into two major types, non-small cell type and small cell type, among which non small cell lung cancer predominates (85%). Adenocarcinoma

is the most common histological type of non small cell carcinoma⁽²⁾.

Recent studies have demonstrated that hypoalbuminemia and low albumin globulin ratio are important predictors of long term mortality in several cancers including gastric cancer, colon and breast cancer.⁽³⁾

Jaffri et al introduced an inflammation based prognostic system in advanced non small cell lung cancer, named as advanced lung cancer inflammation index, taking into account parameters like body mass index (BMI), serum albumin and neutrophil lymphocyte ratio. Later usefulness of ALI was reported in small cell cancer, cancer of oesophagus and B cell lymphoma.⁽⁴⁾

Serum total protein has different components such as albumin, globulin, interleukins, inflammatory proteins and cytokines⁽⁵⁾. Among these the major constituents are albumin and globulin which have been known to play a vital role in inflammatory processes⁽³⁾. Low albumin to globulin ratio is an accepted clinical parameter in multiple myeloma and other immunoproliferative diseases such as lymphoma.^(5,6) Alterations in both albumin and globulin levels in serum have been independently associated with numerous chronic illnesses. Increased serum globulin values are observed in various malignancies, chronic liver disease, nephrotic syndrome, collagen vascular diseases, diabetes mellitus and many other diseases.^(7,8)

To the best of our knowledge, studies on albumin globulin ratio in lung cancer patients has not been carried out in our patients.

Materials and Methods

This study was a retrospective analysis conducted in the department of pulmonary Medicine in a tertiary care centre in Kerala. The case records of 21 patients histologically diagnosed as lung cancer in the department of pulmonary medicine were analysed. Clinical details of patients were noted. Blood samples were collected for testing of total protein and albumin before starting treatment. All samples were analysed at an accredited laboratory. Patients with comorbidities that could alter albumin

globulin ratio such as chronic liver disease, renal disease and other chronic inflammatory diseases were excluded from the study. Histological type of lung cancer, serum levels of albumin and globulins were noted. Albumin-globulin ratio (AGR) was calculated using the equation $AGR = \frac{\text{Albumin}}{\text{Total protein} - \text{Albumin}}$. Analysis of data was done. Patients with chronic diseases likely to have altered serum albumin or globulin levels such as chronic liver disease, diabetic nephropathy and chronic renal failure were excluded from the study

Results

The total number of patients included in the study was 21, out of which 14 were males and 7 were females. The most common histopathological type of lung cancer observed in the study was adenocarcinoma.(14/21). Other types were squamous cell carcinoma (3), small cell carcinoma (1), carcinoid tumor (1) and poorly differentiated cancer (2). Albumin globulin ratio was < 1 in 14 patients. In another 3 patients the ratio was 1.03. Serum globulin was elevated (>3.5) in nine patients. Serum albumin was low (<3.5) in fourteen patients. Total protein was increased above normal (>7) in two patients in whom globulin was very high (>5).

Table.1

Sl no	Age	Sex	Total protein (TP) g/dL	Albumin (A) g/dL	TP-A	AG ratio= A/(TP-A)
1	55	M	7.1	4.4	2.7	1.63
2	71	F	6.6	3.8	2.8	1.35
3	59	M	6.6	3.9	2.7	0.69
4	75	M	6.6	2.9	3.7	0.78
5	24	F	8	2.8	5.2	0.54
6	52	M	7	2.3	4.7	0.49
7	67	M	7.2	2.8	3.4	0.82
8	57	F	7.9	3.3	4.6	0.72
9	48	F	7.2	3.5	3.7	0.94
10	55	M	7	3.4	3.6	0.94
11	70	M	6.7	3.4	3.3	1.03
12	75	M	7.8	4.7	3.1	1.52
13	68	M	6.9	3.5	3.4	1.03
14	60	F	6.7	3.4	3.3	1.03
15	55	M	7.1	3	4.1	0.8
16	65	M	7	4.2	2.8	1.5
17	75	M	5.7	2.6	3.1	0.84
18	60	M	6.3	3	3.3	0.91
19	65	F	7.5	3.9	3.6	0.92
20	50	M	9	3.1	5.9	0.53
21	65	F	5.7	2.6	3.1	0.83

Discussion

Duran et al in their study in patients with histological diagnosis of lung adenocarcinoma have reported that low levels of pre treatment albumin globulin ratio is an independent and significant predictor of long term mortality.⁽⁵⁾ Zhou et al reported that in patients with small cell lung cancer, those with high albumin globulin ratio had higher overall survival than those with low albumin globulin ratio.⁽⁹⁾ Suh et al reported that patients with low albumin globulin ratio are at risk for increased cancer mortality as well as cancer occurrence. Another observation is that patients with low albumin globulin ratio are at increased risk of all types of cancers⁽¹⁰⁾. Increase in globulin content rather than fall in albumin is likely to be more significant contributor to the clinical implications of low A:G ratio in cancer patients, highlighting the role of immunoglobulins in the pathogenesis and complications of lung cancer.

In 1863, Rudolph Virchow, the father of pathology speculated about an association between chronic inflammation and cancer.⁽¹¹⁾ But this thought gained momentum only in the last decade. Increasing evidences support the role of systemic inflammatory response in initiation and progression of cancer. Both cell mediated immunity and humoral immune response is important in the host inflammatory response that orchestrates the initiation, progression and metastasis of tumors.

Immunoglobulins are a family of glycoproteins synthesised in the body in response to antigenic stimulation. The five groups of immunoglobulins are Ig A, IgG, IgM, IgD and IgE. Individual components of immune globulins are identified by serum electrophoresis. Each immunoglobulin molecule is composed of two light chains and two heavy chains. Hyperglobulinemia can be polyclonal, monoclonal, or overproduction of either light chains or heavy chains alone. Among the five immunoglobulin groups, IgG is a family of glycoproteins essential for defending the body against invading pathogens and their toxic products. The antibody constant domain of IgG potentiates pro inflammatory pathways to protect against invading

pathogens.⁽¹²⁾ The pro inflammatory pathways involved are activation of immune effector cells via specific Fc receptors and activation of complement pathway. Immunoglobulins thus have a protective role in infections. These protective antimicrobial molecules may be targeted to normal cellular components giving rise to autoimmune reactions with disastrous consequences. Similar responses are seen frequently in various cancers. A broad spectrum of auto antibodies is found to be associated with certain manifestations of paraneoplastic syndromes. It is observed that certain autoimmune diseases are associated with increased risk of cancer when compared to general population. Examples are systemic lupus erythematosus associated with increased risk of non-hodgkins lymphoma, lung carcinoma, hepatocellular cancer and thyroid malignancies. The presence of autoantibodies in cancer patients is likely to be part of the defensive immune response against the developing tumour. Autoantibodies have attracted interest as potential biomarkers reflecting the nature of malignant process in cancers. A few auto antibodies have been assessed as prognostic biomarkers. One of the most extensively studied tumour associated autoantibody is anti p53 which has been variably linked to prognosis in different reports.⁽¹³⁾

The frequency and intensity of serologic response to antigens show significant variability attributable to intrinsic tumour features such as histologic grade, stage of tumour and molecular subtype as well as host immune and general health conditions. A recent report supports the view that cancer can trigger acquired humoral immunity. The previous concept was that immunoglobulins were produced by plasma cells and B lymphocytes only. Later it was proven that many cancer cells such as breast cancer cells, colorectal cancer cells, prostate cancer cells, papillary thyroid cancer cells, soft tissue tumours, human umbilical endothelial cells, testicular spermatogenic cells, epididymal epithelial cells, human and mouse neurons and eyes also produce immunoglobulins.⁽¹⁴⁾ A study by Wang et al confirmed the expression of IgG in a number of

cancer cells Now it is established that IgG secreted by human cancers promoted growth and survival of tumour cells. IgG detected in different types of malignant tumours including soft tissue tumors was found to correlate with tumour grade and proliferation markers^(15,16)

It was established that cancer derived IgG plays a role in cell growth and proliferation and down regulation of IgG suppresses the growth and multiplication of tumour cells and causes arrest of cell cycle in S phase.⁽¹⁵⁾ IgG induced growth and proliferation of cancer cells is mediated via reactive oxygen species (ROS) . ROS can promote many aspects of tumour development and progression. These can be classified into four biological processes. (A) ligand independent receptor tyrosine kinase (RTK) activation and ERK ½ activation mediated cellular proliferation. (B) evasion of apoptosis via nuclear factor kappa Band phosphatidylinositol- 3 kinase activation (C) angiogenesis by vascular endothelial growth factor and angiopoietin (D) tissue metastasis and invasion via metalloproteinase secretion. Metastasis and invasion are two major causes of cancer related mortality. Metastasis is a complex process involving various proteins which operate on cancer cells after detaching from the primary site, infiltrate into lymphatics and vessels anchoring on to endothelium, induce angiogenesis and intrude into surrounding matrix to establish growth at metastatic site. Jiang et al have studied the expression of immunoglobulin G genes in lung cancer cell lines including squamous cell and adenocarcinoma and found that metastasis associated gene 1(MTA1) appeared to be coexpressed with Ig G in lung cancer cells. The rate of IgG expression correlated with MTA1 and lymph node metastasis⁽²⁾

Limitations of the Study

This is not a prospective study. It is a retrospective study that made use of the recorded data. Follow up study of the patients to find out the correlation of A:G ratio with prognosis or survival could not be assessed .

Conclusion

Cancer related inflammation has been a subject of interest in the field of cancer research. This study supports the recently changed concept that cancer cells are capable of producing immunoglobulins as against the older concept that immunoglobulins are produced by B cells alone. The host inflammatory response in cancer operates via humoral and cell mediated immunity. Tumorigenic factors such as proinflammatory cytokines, proangiogenic and invasion promoting factors, antiapoptotic factors, enzymes, prostaglandins, as well as iNOS have been identified as crucial mediators of inflammation in tumor genesis. Modern anticancer therapies aim to suppress such inflammatory mediators such as TNF α and IL1. Another novel approach in cancer therapy aims intravenous gamma globulin administration, success of which in animal models, undescores the role of immunoglobulins in cancer pathogenesis and progression.

Source of support- Nil

Conflict of interest- Nil

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010 Oct;60(5):277–300.
2. Jiang C, Huang T, Wang Y, Huang G, Wan X, Gu J. Immunoglobulin G expression in lung cancer and its effects on metastasis. *PloS One.* 2014;9(5):e97359.
3. Azab B, Kedia S, Shah N, Vonfrolio S, Lu W, Naboush A, et al. The value of the pretreatment albumin/globulin ratio in predicting the long-term survival in colorectal cancer. *Int J Colorectal Dis.* 2013 Dec;28(12):1629–36.
4. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. *BMC Cancer.* 2013 Mar 27;13:158.
5. Duran AO, Inanc M, Karaca H, Dogan I, Berk V, Bozkurt O, et al. Albumin-globulin

- ratio for prediction of long-term mortality in lung adenocarcinoma patients. *Asian Pac J Cancer Prev APJCP*. 2014;15(15):6449–53.
6. Busher JT, Walker HK, Hall WD, Hurst JW. Serum albumin and globulin, *Clinical Methods: the History, Physical, and Laboratory Examinations*, 19903rd edition Boston, MA Butterworths (pg. 497-499).
 7. Kyle RA. Sequence of testing for monoclonal gammopathies. *Arch Pathol Lab Med*. 1999 Feb;123(2):114–8.
 8. Dispenzieri A, Gertz MA, Therneau TM, Kyle RA. Retrospective cohort study of 148 patients with polyclonal gammopathy. *Mayo Clin Proc*. 2001 May;76(5):476–87.
 9. Zhou T, He X, Fang W, Zhan J, Hong S, Qin T, et al. Pretreatment Albumin/Globulin Ratio Predicts the Prognosis for Small-Cell Lung Cancer. *Medicine (Baltimore)*. 2016 Mar;95(12):e3097.
 10. Suh B, Park S, Shin DW, Yun JM, Keam B, Yang H-K, et al. Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults. *Ann Oncol Off J Eur Soc Med Oncol*. 2014 Nov;25(11):2260–6.
 11. Heidland A, Klassen A, Rutkowski P, Bahner U. The contribution of Rudolf Virchow to the concept of inflammation: what is still of importance? *J Nephrol*. 2006 Jun;19Suppl 10:S102-109.
 12. Lux A, Aschermann S, Biburger M, Nimmerjahn F. The pro and anti-inflammatory activities of immunoglobulin G. *Ann Rheum Dis*. 2010 Jan;69Suppl 1:i92-96.
 13. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. *Autoimmun Rev*. 2017 Oct;16(10):1049–57.
 14. Hu F, Zhang L, Zheng J, Zhao L, Huang J, Shao W, et al. Spontaneous Production of Immunoglobulin M in Human Epithelial Cancer Cells. *PLOS ONE*. 2012 Dec 12;7(12):e51423.
 15. Wang J, Lin D, Peng H, Huang Y, Huang J, Gu J. Cancer-derived immunoglobulin G promotes tumor cell growth and proliferation through inducing production of reactive oxygen species. *Cell Death Dis*. 2013 Dec;4(12):e945.
 16. Chen Z, Huang X, Ye J, Pan P, Cao Q, Yang B, et al. Immunoglobulin G is present in a wide variety of soft tissue tumors and correlates well with proliferation markers and tumor grades. *Cancer*. 2010 Apr 15;116(8):1953–63.