IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 2 Ver. XII (Feb. 2016), PP 65-69
www.iosrjournals.org

Inflammatory cells, the Lymphocyte to Monocyte Ratio and the Lymphocyte to Eosinophil Ratio as inexpensive prognostic/diagnostic markers of Cancer

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Abstract: *The link between inflammation and the development of cancer has gained interest in recent years. The interplay between chronic inflammation and cancer is very complex.In the present stud the alterations in lymphocytes ,monocytes and eosionophils counts in four major types of cancer namely Ovarian cancer , Colon cancer, Liver cancer and Prostate cancer was studied . The levels of the inflammatory cells were then compared with the counts in normal subjects. Upon comparison a statistically significant increase in monocyte and eosinophil levels and significant decrease in lymphocyte levels was observed. The LMR and LER in normal and cancer subjects were also calculated. These alterations of inflammatory cells can be inexpensive diagnostic /prognostic markers in cancer.*

Key words: *Lymphocyte, Monocytes, Eosinophils, Prostate cancer, Ovarian Cancer*

I. Introduction

Inflammation has been identified to be a critical component of tumor progression. With growing evidence on the role of inflammation in Cancer biology, the systemic inflammatory response has been postulated as having prognostic significance in wide range of cancer types. Inflammatory cells can release growth and survival factors promoting angiogenesis and lymphogenesis, stimulate DNA damage and promote tumor evasion of the host defense mechanism (De visser *et al* ., 2006). Although the inflammatory response can be expected to have tumor suppressive role , cancer patients often lack sufficient inflammatory response (Finn , 2012). For different solid tumors as well as Lymphomas, inflammation parameters ,including Leukocytes , Neutrophils , Lymphocytes and C-reactive protein have been associated with high mortality rates (Mohri *et al.,* 2010; Cao *et al* ., 2012).

The inflammatory component of a developing tumor may include a diverse leukocyte population including neutrophils ,eosinophils ,mast cells and lymphocytes ,all of which are capable of producing a wide variety of mediators (Wahl *et al* ., 1998).By the release of specific chemokines ,the tumor microenvironment controls leukocyte migration and other functions of these cells after their arrival at the tumor site . The autocrine production of chemokines by tumor cells attracts the inflammatory cells and increase their survival, proliferation and dissemination (Balkwill *et al.,* 2004).

In addition to absolute counts of inflammation parameters , the neutrophil to lymphocyte ratio (NLR) has been identified as an independent prognostic factor for overall survival in various types of cancer (Walsh *et al.,* 2005 ; Zhang *et al.,* 2012; Pichler *et al.,* 2013 ; Skandera *et al*., 2013). In various types of cancers for example , Breast cancer, melanoma and lymphoma , innate immune cells like granulocytes , macrophages and mast cells correlate with increased angiogensis and /or poor prognosis , which in past explained by upregulation of cyclo oxygenase -2 or suppression of anti-tumor adaptive immune response (Leek *et al.,* 1996 ; Liu *et al.,* 2001; Schoppman *et al.,* 2002; Dannenberg and Subbaramanian , 1997 ; Ribatti *et al.*,2003).The neutrophil – lymphocyte ratio, the platelet- lymphocyte ratio ,the c-reactive protein or fibrinogen levels have been proposed as prognostic parameters that adequately reflect the systemic inflammatory response in cancer (Troppan *et al.,* 2014).Thus the host response to malignant tumors comprises not only local changes in tumor microenvironment but also systemic effects .These haematological findings significantly correlate with advanced tumor stage and poor disease prognosis.

II. Materials and Methods

Subjects

A total of 120 patient histologically confirmed of the four major types of cancer namely Colon, Liver, Ovarian and Prostate cancer , 30 numbers in each category, were involved in the study after obtaining an informed consent for participation in the study and after obtaining ethical clearance for the same.
All patients were treated at V.S.cancer Hospital, Chennai,TamilNadu, India.

Samples

Blood was collected from all patients in suitable vials. The samples were collected after obtaining proper Institutional ethical clearance for the study.

Blood cell counts

The total count , Differential count and Haemoglobin % were calculated by routine laboratory procedure. From the blood counts the Lymphocyte to Monocyte Ratio (LMR) and the Lymphocyte to Eosinophil Ratio (LER) was calculated.

Statistical Analysis

Statistical analyses were carried out using the SPSS statistical software. The results were expressed as Mean ± Standard deviation. The significance of differences between groups was determined by the Student unpaired t test. Values of $p< 0.05$ were considered as significant.

III. Results

The Total Count , Differential Count and Hb % was evaluated in all blood samples and compared with the respective values in normal subjects

Colon cancer

A statistically significant decrease in the total counts was observed in colon cancer ($p < 0.05$, $p= 0.037$) . A significant decrease in lymphocyte levels was observed ($p < 0.05$, $p =0.019$) . A highly significant increase in monocyte levels ($p < 0.001$) was also observed in colon cancer samples . Even Eosinophil count showed a statistically significant increase ($p < 0.001$) (Table : 1)

Prostate cancer

In prostrate cancer there was no significant change in the total count . However there was a significant increase in monocyte ($p< 0.001$, $p = 0.0007$) and eosinophil levels $p < 0.001$. Lymphocyte levels showed a statistically significant decrease ($p = 0.01$, $P < 0.05$).There was no significant change in the levels of RBC and Hb % .(Table : 2)

Ovarian cancer

There was no significant change in the RBC count and HB %.However was a statistically significant increase in the monocytes levels ($p<0.05$, $p=0.015$) in the ovarian cancer sample. There was also a significant increase in the eosinophil count in the ovarian cancer sample ($p=0.003$, $p<0.05$) .(Table: 3)

Liver Cancer

In liver cancer sample also there was a significant increase in Monocytes levels ($p=0.01$; $p=0.05$) and highly significant increase in eosinophil count (Table : 4)

Lymphocyte to Monocyte Ratio (LMR) and Lymphocyte to Eosinophil Ratio (LER)

LMR and LER showed a significant decrease in cancer subjects than normal subjects (Table 5 & 6)

Haematological parameters of Cancer patients compared with normal subjects.
Values presented as mean cell count ± SD

	Table :1 Colon Cancer						
	RBC	**NEUTROPHILS**	**LYMPHOCYTES**	**EOSINOPHILS**	**HB**	**MONOCYTES**	**TC**
CANCER PATIENTS	4.327 ± 0.631	62.363 ± 10.14	27.364 ± 8.215	4.545 ± 2.109	12.08 ± 2.26	4.313 ± 1.99	6,275 ± 1937.87
NORMAL SUBJECTS	4.08 ± 0.656	64.818 ± 9.46	33.818 ± 9.42	1.273 ± 0.456	12.327 ± 1.98	2.3125 ± 1.14	8,519 ± 3631.57
	NS	NS	p = 0.019 < 0.05	p< 0.001	NS	p <0.001	p=0.037 <0.05

	Table : 2 Prostate Cancer						
	RBC	**NEUTROPHILS**	**LYMPHOCYTES**	**EOSINOPHILS**	**HB**	**MONOCYTES**	**TC**
CANCER PATIENTS	4.267 ± 0.672	65.5 ± 5.19	26.125 ± 5.35	3.875 ± 1.204	12.763 ± 1.586	4.5 ± 0.76	9,525 ± 2614.66
NORMAL SUBJECTS	3.963 ± 0.704	63.13 ± 10.6	34.5 ± 11.05	1.375 ± 0.5	12.613 ± 1.765	2.25 ± 1.281	9,500 ± 4842.67
	NS	NS	p=0.01	p< 0.001	NS	0.0007 p< 0.001	NS

	Table:3 Ovarian Cancer						
	RBC	**Neutrophils**	**Lymphocytes**	**Eosinophils**	**HB**	**Monocytes**	**TC**
CANCER LEVEL	4.055 ± 0.34	58.625 ± 9.32	35.125 ± 7.04	4.33 ± 1.86	11.6 ± 1.90	4 ± 1.8	6825 ± 2327.94
NORMAL LEVEL	4.175 ± 0.002	64 ± 11.45	34.5 ± 11.44	1.38 ± 0.517	12.61 ± 1.83	2 ± 1.3	9550 ± 48.42
	NS	NS	NS	p<0.001,p=0.0009	NS	p=0.015	NS

	Table:4 Liver Cancer						
	RBC	**Neutrophils**	**Lymphocytes**	**Eosinophils**	**HB**	**Monocytes**	**TC**
CANCER LEVEL	4.78 ± 0.67	64 ± 4.24	29 ± 5.35	4.25 ± 0.5	13.48 ± 1.86	5 ± 0.8	6550 ± 1215.2
NORMAL LEVEL	4.38 ± 0.67	66.8 ± 3.86	31.5 ± 3.7	1.25 ± 0.5	13.2 ± 2.04	2.5 ± 1.29	2875.6 ± 2490
	NS	NS	NS	p=0.0001	NS	p=0.016	NS

Table : 5 LMR in normal and cancer subjects

	Liver cancer	**Colon cancer**	**Ovarian Cancer**	**Prostate cancer**
Normal	12.6 : 1	14.6 : 1	17.3 : 1	15.3 : 1
Cancer	5.8 : 1	6.3 : 1	8.8 : 1	5.8 : 1

Table: 6 LER in normal and Cancer Subjects

	Liver cancer	**Colon cancer**	**Ovarian Cancer**	**Prostate cancer**
Normal	25.2 : 1	26.6 : 1	25 : 1	25 : 1
Cancer	6.8 : 1	6.02 : 1	8.1 : 1	6.7 : 1

IV. Discussion

The influence of cancer and inflammation was well known but until now tumor –inflammation interaction has not been completely explained.

Variations in systemic inflammatory cell amount might be a valuable prognostic marker for stratifying patients at risk for tumor recurrence in cancer (Gomz *et al*.,2008, Cho *et al*., 2009, Idowu *et al.,* 2012; Kwon *et al.,* 2012;Rraungkaemanee *et al.,*2012)

Earlier studies have reported that a lower lymphocyte count was associated with increased cancer mortality , especially from hepatoma, pancreatic carcinoma, colorectal,breast and prostate cancer .(Fogar *et al.,*2006; Huang *et al.,* 2003; Lissoni *et al.,* 2006).

The host response to malignant tumors comprises not only local changes in tumor microevironment , but also systemic effects. These haematological conditions significantly correlate with the advancement of tumor. It is intresting to know how tumor development contributes to alterations in the number of circulating leucocytes. One possible mechanism is the production of soluble factors such as granulocytes and macrophage colony stimulating factor (GM-CSF) by tumor cells,capable of mobilizing precursors in the bone marrow or vascular endothelial growth factor (VEGF) and interleukin -6 ,both of which alter cell differentiation (Pinzon – Charry *et al.,* 2005).

Lymphocyte depletion with consequent depression of innate cellular immunity is severe clinical problem that can develop during cancer progression and cytoreductive therapies. Lymphophenia results from tumor induced mechanisms that include impairment of antigen presentation ,activation of negative costimulatory signals , and production of immunosuppressive factors,resulting in a marked decrease in T-helper lymphocytes (Walsh *et al.,* 2005 & Croci *et al.,* 2007).

Another reason for these alterations might be accumulation of genetic failures over time ,leading to oncogenic activation ,simultaneously , inactivation of tumor suppressor genes ,which are responsible for higher transcription of inflammatory mediators resulting in an inflammatory condition in the tumor cell environment.

Further tumor related leucocytes especially monocytes , are main regulators of cancer inflammation and and have an essential role in systemic inflammatory response to tumor disease (Allavena *et al.,* 2008; Mantovani *et al.,* 2008) .

There is less adequate data regarding Lymphocte to monocyte ratio in solid tumors as a prognostic marker. The LMR and LER might be a good reflection of both lymphophenia that is a surrogate marker of weak immune response and an increased monocyte count , suggestive of high tumor burden.

V. Conclusion

Cancer patients often develop para neoplastic syndromes. These conditions can be useful predictors of response to treatment and survival.

LMR, LER can be obtained from the data already routinely available, without additional costs. Further understanding of the mechanisms giving rise to these conditions may contribute to the development of new therapeutic strategies in cancer and could benefit disease prognosis.

Conflict of Interest

No potential conflicts of interest were disclosed.

Acknowledgements

I thank Dr.S.Subramaniam , Managing Director ,V.S.Hospital , Chetpet , Chennai, for his support for the work.

References

[1]. De Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer. 2006;6 (1:24–37.
[2]. Cao Y, Shi YX, Chen JO, Tan YT, Cai YC, Luo HY, Qiu MZ, Cai XY, Jin Y, Sun YL, Jiang WQ. Serum C- reactive protein as an important prognostic variable in patients with diffuse large B cell lymphoma. Tumour Biol. 2012;33 (4:1039–1044.
[3]. Mohri Y, Tanaka K, Ohi M, Yokoe T, Miki C, Kusunoki M. Prognostic significance of host- and tumor-related factors in patients with gastric cancer. World J Surg. 2010;34(2:285–290.
[4]. Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Ann Oncol. 2012. pp. viii6–viii9.
[5]. Wahl LM, Kleinman HK. Tumor-associated macrophages as targets for cancer therapy. J Natl Cancer Inst 1998; 90: 1583-4.
[6]. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer. 2004;4:540–550.
[7]. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg oncol. 2005;91 (3:181–184.
[8]. Zhang DS, Wang DS, Wang ZQ, Wang FH, Luo HY, Qiu MZ, Wang F, Li YH, Xu RH. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Med Oncol. 2012;29 (5:3092–3100.
[9]. Pichler M, Hutterer GC, Stoeckigt C, Chromecki TF, Stojakovic T, Golbeck S, Eberhard K, Gerger A, Mannweiler S, Pummer K, Zigeuner R. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. Br J Cancer. 2013;108 (4:901–907
[10]. Pichler M, Hutterer GC, Stojakovic T, Mannweiler S, Pummer K, Zigeuner R. High plasma fibrinogen level represents an independent negative prognostic factor regarding cancer-specific, metastasis-free, as well as overall survival in a European cohort of non-metastatic renal cell carcinoma patients. Br J Cancer. 2013;109 (5:1123–1129.
[11]. Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, Glehr M, Zacherl M, Stojakovic T, Gerger A, Leithner A. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013; 108 (8:1677–1683.
[12]. Szkandera J, Pichler M, Gerger A, Leithner A. Reply: comment on 'Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients'. Br J Cancer. 2013;108 (12:2627.
[13]. Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J, Harris AL. Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma.Cancer Res. 1996;56 (20:4625–4629
[14]. Liu CH, Chang SH, Narko K, Trifan OC, Wu MT, Smith E, Haudenschild C, Lane TF, Hla T. Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. J Biol Chem. 2001;276 (21:18563–18569.
[15]. Schoppmann SF, Birner P, Stöckl J, Kalt R, Ullrich R, Caucig C, Kriehuber E, Nagy K, Alitalo K, Kerjaschki D. Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. Am J Pathol.2002;161 (3:947–956.
[16]. Dannenberg AJ, Subbaramaiah K. Targeting cyclooxygenase-2 in human neoplasia: Rationale and promise. Cancer Cell. 2003;4 (6:431–436.
[17]. Ribatti D, Ennas MG, Vacca A, Ferreli F, Nico B, Orru S, Sirigu P. Tumor vascularity and tryptase-positive mast cells correlate with a poor prognosis in melanoma. Eur J Clin Invest. 2003;33 (5:420–425.
[18]. Troppan K, Deutsch A, Gerger A, et al (2014). The derived neutrophil to lymphocyte ratio is an independent prognostic factor in patients with diffuse large B-cell lymphoma. Br J Cancer, 110, 369-74.
[19]. Subbaramaiah K, Telang N, Bansal MB, Weksler BB & Dannenberg AJ 1997 Cyclooxygenase-2 gene 842 expression is upregulated in transformed mammary epithelial cells. Annals of the New York Academy of 843 Sciences 833 179-185.
[20]. Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, Prasad KR (2008) Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma.*World J Surgery* **32**(8): 1757–1762.
[21]. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, Lee K (2009) Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer Immunol Immunother* **58**(1): 15–23.
[22]. Idowu OK, Ding Q, Taktak AF, Chandrasekar CR, Yin Q (2012) Clinical implication of pretreatment neutrophil to lymphocyte ratio in soft tissue sarcoma. *Biomarkers* **17**(6): 539–544.

[23]. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, Park KJ, Roh MS, Kim SG, Kim HJ, Lee JH (2012) Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. *Biomarkers* **17**(3): 216–222.
[24]. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Thavaramara T (2012) Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. *J Gynecol Oncol* **23**(4): 265–273.
[25]. Fogar P, Sperti C, Basso D, et al. Decreased total lymphocyte counts in pancreatic cancer: An index of adverse outcome. Pancreas 2006; 32: 22-8.
[26]. Huang ZS, Chien KL, Yang CY, Wang CH, Chang TC, Chen CJ. Peripheral differential leukocyte counts and subsequent mortality from all diseases, cancers, and cardiovascular diseases in Taiwanese. J Formos Med Assoc 2003; 102: 775-81.
[27]. Lissoni P, Fumagalli L, Brivio F, et al. Cancer chemotherapyinduced lymphocytosis: a revolutionary discovery in the medical oncology. J Biol Regul Homeost Agents 2006; 20: 29-35
[28]. Pinzon-Charry A, Ho CSK, Laherty R, *et al*. A Population of HLADR + immature cells accumulates in the blood dendritic cell compartment of patients with different types of cancer. Neoplasia 2005; 7: 1112-22
[29]. Croci DO, Fluck MFZ, Rico MJ, Matar P, Rabinovich GA, Scharovsky OG. Dynamic cross-talk between tumor and immune cells in orchestrating the immunosuppressive network at the tumor microenvironment. Cancer Immunol Immunother 2007; 56: 1687-1700.
[30]. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil- Lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005; 91: 181-4
[31]. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. *Nature* **454**(7203): 436–444.
[32]. Allavena P, Garlanda C, Borrello MG, Sica A, Mantovani A (2008) Pathways connecting inflammation and cancer. *Curr Opin Genet Dev* **18**(1): 3–10.