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Total Peripheral Lymphocyte Count in Malignant Tumors: An Index of Prognostication

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The present study was planned to explore the influence of total peripheral lymphocyte count in cancer patients and to ascertain its prognostic significance. 100 cases were divided into 2 groups: test group comprised of 75 cancerous cases and control group of 25 cases who did not suffer from any problem known to alter the immune status. After a detailed clinical history and examination, routine investigations and certain specific investigations like ultra-sonography, intravenous pyelography, computed tomography, fine needle aspiration cytology and histopathology were performed. Total Leukocyte Count (TLC) using Turk's fluid was performed along with differential count from peripheral smear and Total Peripheral Lymphocyte Count (TPLC) was calculated by the formula: TPLC = TLC × percentage of lymphocytes in differential count. Majority of the malignant cases belonged to the fifth decade. Histologically, carcinoma was most frequent, 92.0% cases, followed by sarcoma, 6.6% and melanoma, 1.3% cases. The mean TPLC in the control group was 2759.12±955.7 and it was significantly depressed in all the malignant cases. In breast carcinoma, TPLC was found to decrease with disease progression and was stage dependent. TPLC shows promise as a diagnostic and prognostic indicator of malignancy.

Key words: Malignant tumors, TPLC, prognostication

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INTRODUCTION

Ehrlich (1909) was the first to suggest that immunity played a role in defence against cancer. Whatever progress has been made in our knowledge of cancer, an understanding of immunological approach of the behavior of the tumors and development of new methods for treating them still remains obscured. However, it is generally accepted that depression of immune response in patients suffering from neoplastic disease contributes to the pathogenesis of cancer.

The relationship between cancer and cellular immunity has been subject of numerous studies during the last few decades. Yang and Ansell (2009) reported the role of lymphocytes in resistance to tumors. In recent years much significance has been attached to correlate the prognosis of cancer with lymphocyte counts of peripheral blood. Papatestas *et al.* (1976) observed an inverse correlation between stage of malignant tumors and the lymphocyte count and proposed that the pre-treatment lymphocyte levels was an index of the host immune competence. Epidemiologic data have suggested decreased incidence of malignancies in patients with elevated baseline (homeostatic) levels of Natural Killer (NK) cells activity (Block and Markovic, 2009).

Lymphocyte level is an index of cell-mediated immunity which is important in host defense against cancer. But it is surprising that a simple test such as peripheral lymphocyte count could be correlated with clinical stages and survival results in patients with different tumors. Regarding the latter, lymphocyte count has prognostic values in patients with cancer of the bone, Ewing's sarcoma, breast, colon, kidney, neuroblastoma, uterine cervix and other sites (Ray-Coquard *et al.*, 2009). In general, higher lymphocyte counts before therapy correlated with longer survival (Ray-Coquard *et al.*, 2009).

Nemoto *et al.* (1974) reported similar TPLC in both advanced and early breast carcinoma which is contradictory to the study of Ray-Coquard *et al.* (2009) who observed decreased TPLC in breast cancer patients with advanced stages as compared to those with early disease.

In view of the contradictory results in the existing literatures, the present study was planned to explore the influence of total peripheral lymphocyte count in cancer patients and to ascertain its prognostic significance.

MATERIALS AND METHODS

The present study on 100 cases was carried out in patients attending the outpatient and inpatient departments of Surgery and Pathology of J. N. Medical College Hospital, AMU, Aligarh.

The patients were divided into 2 groups: test group comprised 75 patients suffering from malignant tumor of different organs and the control group comprised 25 patients who did not suffer from any problem known to alter the immune status. After a detailed clinical history and a thorough physical examination, routine haematological investigations, X-ray chest, electro-encephalography and urine examinations were performed. Specific investigations like liver function test, ultra-sonography, intravenous pyelography, computed tomography, fine needle aspiration cytology and histopathology were done depending upon the organ involved.

Total Leucocyte Count (TLC) using Turk's fluid was performed along with differential count from peripheral blood smear. Total Peripheral Lymphocyte Count (TPLC) was calculated by the formula: TPLC = TLC × percentage of lymphocytes in differential leucocyte count.

RESULTS

Majority of the cases, 29.3% were found in the fifth decade followed by 24.0% in the fourth decade, with mean age of 43.9 years and male:female sex ratio of 0.9:1.

Out of the total 75 malignant cases, there were 65 cases of carcinoma, 5 of sarcoma, 4 of lymphoma and one of malignant melanoma.

The most common malignant tumor was carcinoma breast, 25 cases (33.3%), followed by genitourinary tract carcinoma, 19 cases (25.3%), hepatobiliary carcinoma, 10 cases (13.3%), gastro-intestinal tract carcinoma, 8 cases (10.7%), oral carcinoma, 3 cases (4.0%), sarcoma, 5 cases (6.7%), lymphoma, 4 cases (5.3%) and malignant melanoma 1 case (1.3%). The most common malignancy in males was genitourinary tract carcinoma, 10 cases followed by gastrointestinal tract carcinoma in 7 cases whereas the most common occurrence in females was carcinoma breast, 22 cases followed by 8 cases of hepatobiliary carcinoma.

On calculation of absolute lymphocyte count in different age groups, it was noted that the mean TPLC in the first and second decades of control group was 3031.3 and 3138.6, respectively while it was lower in the study group i.e., 1259.0 and 1339.5 in the first and second decades of life, respectively (Table 1).

Table 1: Age wise distribution of mean total peripheral lymphocyte count

	Mean TPLC	
Age group (years)	Control group	Study group
0-10	3031.3	1259.0
11-20	3138.6	1339.5
21-30	2367.1	2128.8
31-40	3954.0	2632.6
41-50	3337.5	1918.2
51-60	2035.4	1876.3
>60	1840.0	1637.8

Table 2: Total peripheral lymphocyte count in malignant tumors of different histological types

Tumor	No. of cases	Mean TPLC	p-value
Control group	25	2759.1	-
Carcinoma	69	2036.8	<0.05
Sarcoma	5	2247.2	<0.05
Melanoma	1	1974.0	-

Table 3: Total peripheral lymphocyte count in different stages of breast carcinoma

Tumor	No. of cases	Mean TPLC	p-value
Control group	25	2759.1	-
Carcinoma breast	25	1909.5	-
Stage-I	8	2260.4	<0.05
Stage-II	4	2158.0	<0.05
Stage-III	9	1886.0	<0.05
Stage-IV	4	1334.0	<0.05

On evaluation of mean total peripheral lymphocyte count in malignant tumors of different histological types, it was found to be 2036.8 in carcinoma, 2247.2 in sarcoma and 1974 in melanoma while in the control group mean TPLC was 2759 (Table 2).

Out of the 25 cases of carcinoma breast, 8 cases were in stage-1 disease, 4 in stage-II, 9 in stage-III and 4 were in stage-IV disease (TNM classification). Mean TPLC in stage-I disease was 2260.4 and 1334 in stage-IV. Thus with increasing stage of the disease, a marked depression of TPLC was seen, which was statistically significant ($p<0.05$) (Table 3). A significant decrease in TPLC in carcinoma breast was found in the 6th decade, when age corrected TPLC count was performed.

Out of 18 cases of genitourinary tract carcinomas, there were 6 cases of renal cell carcinoma, 2 carcinoma prostate, 4 carcinoma penis, 3 carcinoma urinary bladder and one case of testicular carcinoma. The mean TPLC in renal cell carcinoma was 2047.8. It was 1688 in carcinoma prostate, 1569 in carcinoma penis, 1796.7 in carcinoma of urinary bladder and 1625 in cases of testicular carcinoma. Thus the mean TPLC was significantly depressed in all cases of genitourinary tract carcinomas as compared to control group. The depression was more marked in carcinoma penis and prostate and was statistically significant on comparision to control group ($p<0.05$).

We reported 8 cases had carcinoma gall bladder while 2 had carcinoma of periampullary region with obstructive jaundice. The mean TPLC in carcinoma gall bladder was 1692.8 and it was 2080 in carcinoma of periampullary region. The decrease in mean TPLC was more marked in cases of carcinoma gall bladder with secondaries in the liver and was statistically significant when compared to control group ($p<0.05$).

Out of the 8 cases of gastrointestinal tract carcinomas, 4 each had carcinoma stomach and colorectal carcinoma. The mean TPLC in carcinoma stomach was 898.5 and it was 1667.6 in colorectal carcinoma. Thus, we observed that the TPLC in cases of carcinoma stomach was markedly depressed and statistically significant when compared to the control group ($p<0.01$).

There were 3 cases of fibrosarcoma and 1 case each of rhabdomyosarcoma of chest wall and Ewing's sarcoma of right foot. The mean TPLC was 2024 in fibrosarcoma, 2582 in rhabdomyosarcoma and 2342 in Ewing's sarcoma. Thus it was noted that the mean TPLC was significantly depressed in all cases of sarcoma as compared to the control group.

Out of 4 cases of lymphoma, 2 each had Hodgkin's lymphoma and non-Hodgkin's Lymphoma (NHL). The mean TPLC was 1210 in Hodgkin's lymphoma and 8171 in non-Hodgkin's lymphoma. Thus in Hodgkin's lymphoma, the mean TPLC was significantly decreased while in NHL, it was elevated when compared to the control group. One of the cases of NHL was of diffuse well-differentiated lymphocyte predominant variety.

The mean TPLC in the single case of malignant melanoma was 1974 which showed a significant decrease as compared to control group ($p<0.05$).

DISCUSSION

With the advent of new technological advances (e.g., microarray gene expression analysis), it is important to recognize that low cost, standardized, routinely used tests such as a complete blood cell count (CBC) can still provide useful information regarding the behavior of different malignancies, as well as serve as a platform for the development of therapeutic interventions aimed at improving clinical outcomes (Porrata and Markovic, 2010). In the present study, an attempt was made to assess cellular immune responses in cancer patients through assessment of TPLC, as a prognostic factor for survival in cancer.

It is a well known fact that, cancer is a disease of older age group. Maximum incidence of carcinoma was found in the 6th decade of life (39.3%) in this study as compared to Russel *et al.* (2004).

On assessment of TPLC in different cancer patients, the mean TPLC was found to be decreased in all stages of carcinoma breast as compared to control group. A decrease in mean TPLC was also noted with progression of the disease, a finding comparable with reports of Blake-Mortimer *et al.* (2004) who observed that, the decrease in the TPLC was directly proportional to the progress of the disease. Peripheral lymphocyte count was found to be comparatively on the higher side in patients with localized carcinoma breast as compared to carcinoma breast with evidence of metastasis. However, Nemoto *et al.* (1974) observed no change in peripheral

lymphocyte count in patients of carcinoma breast. Lee (1977) has reported that patients with a higher peripheral blood CD8 count experienced superior survival in a cohort of 113 women with metastatic or recurrent breast cancer. Better clinical outcomes associated with high absolute lymphocyte count have been also reported in gastric and head and neck carcinomas (Lee, 1977).

Present study showed significantly decreased mean TPLC in all malignant tumors of genitourinary tract as compared to control group. The decrease was more marked in carcinoma prostate, a finding consistent with Bubenik *et al.* (1970) who observed significant intrinsic deficiency of T-lymphocyte function in clinically localized prostatic carcinoma. But Block and Markovic (2009) reported that decrease in lymphocyte reactivity in urologic carcinoma was caused by serum mediated inhibition and not by an intrinsic cellular defect.

The mean TPLC was significantly depressed in carcinoma gall bladder and periampullary region as compared to control group in this study. Block and Markovic (2009) have also reported suppression of immune response in carcinoma of hepatobiliary region with secondaries.

We also noted decreased TPLC in cases of carcinoma stomach and colorectum, which is in conformity with the study of Block and Markovic (2009). On the contrary, Lee (1977) reported increased immune response in cases of gut carcinoma.

The TPLC in 5 cases of sarcoma was found to be decreased as compared to the control group, a finding consistent with Lee (1977) who reported that cases of advanced sarcoma had significantly lower percentage of lymphocytes in comparision to benign conditions.

In Hodgkin's lymphoma, the mean TPLC was reduced as compared to control group and was statistically significant, a finding concordant with Porrata *et al.* (2002) and Siddiqui *et al.* (2006). The mean TPLC in NHL was increased as compared to the control group, a finding consistent with the studies of Paloczi *et al.* (1987) who suggested that the most important factor for increased TPLC is the increase in the amount of B lymphocytes. Immune anergy-a feature of extensive Hodgkin's disease correlates with the relative depletion of lymphocytes and might be the reason of the encountered hyporeactivity of patients to intradermally injected antigens. It might even be proposed that this very immuno-depletion may have a role in subsequent dissemination of the lymphoma. Regarding NHL, Paloczi *et al.* (1987) contention of increasing B lymphocytosis can be taken forward to include the lymphocytosis caused by free circulating lymphoma cells in addition to reactive B lymphocytes. This circulation and homing of malignant lymphocytes may be a possible explanation of the routinely observed dis-contiguous spread of NHL as compared to Hodgkin's disease.

CONCLUSION

The reduction of total lymphocytes in blood is the main immunologic change in advanced malignancy. The survival of these patients is affected by the number of circulating lymphocytes, suggesting that the immune system plays an important role in carcinoma immunosurveillance and immunoediting. Total peripheral lymphocyte count shows promise as an indicator of prognosis varying with tumor type. Further studies are required to evaluate TPLC as an index influencing disease outcome of the patient.

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