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Research Article

CD4:CD8 RATIO PROGNOSTIC IMPACT IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disease characterized by clonal expansion of B- cells. The clinical course of B-CLL patients is highly variable. Immunosuppression is a prevalent clinical feature in chronic lymphocytic leukemia (CLL) patients. To provide further clarity to this particular phenomenon, we analyzed the T-cell pro le of CLL patient samples within a large cohort and observed that patients with an inverted CD4/CD8 ratio had a shorter time to treatment as well as overall survival. **Material and methods:** This study was conducted over a period of one year on 50 newly diagnosed cases of CLL and 20 control samples from apparently healthy individuals at PGIMS Rohtak. 2 ml EDTA peripheral blood immunophenotyping was performed on 8 Color Flow cytometer BD FACS Canto II (Becton Dickinson, San Jose, CA). The CD panel used CD45, CD19, CD20, CD23, CD5, CD200, CD38, CD4, CD8, CD3, FMC7, CD10, CD79b, Kappa, Lambda. **Results:** There was slight male predominance with male to female ratio of 1.6:1 in our study. Average age of the patients was 60.8 years (range 43-85 years). The mean helper to suppressor ratio (CD4/CD8) of 50 patients with CLL was 1.2±0.28 as compared to the mean of 20 normal volunteers tested at the same period of time was 1.86 ± 0.64 ($p < 0.00$). The low CD4/CD8 ratio found in advanced stages is due to a decrease of the absolute number of CD4 + cells. **Conclusions:** The finding of the present study which is probably of clinical relevance is the fact that immune function parameter at diagnosis seem to have predictive value in patient with CLL in clinical stage III and IV. CD4/CD8 ratio was decreased in advanced form of chronic lymphocytic leukemia and this simple parameter of immune function seem to have a huge prognostic value for patients with CLL and predict the clinical course of the disease.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disease and is characterized by clonal expansion of B- cells. These B cells accumulate in bone marrow and peripheral lymphoid tissues. The clinical course of B-CLL patients is highly variable. Some patients may live years without progression or need for treatment. However, a significant group of B-CLL patients (85%) present with severe immunodeficiency at diagnosis, manifested mostly as hypogammaglobulinemia.[1,2] The staging systems developed by Rai *et al*. and Binet *et al*. are the gold standard methods of prognosis assessment in CLL.[3] Rai stage 0: Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts. Rai stage I: Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal.

Rai stage II: Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are near normal.

Rai stage III: Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal. Rai stage IV: Lymphocytosis plus thrombocytopenia (too few blood platelets), with or without anemia, enlarged lymph nodes, spleen, or liver Stage 0 is considered low risk. Stages I and II are considered intermediate risk. Stages III and IV are considered high risk.[4]Current prognostic factors focus only on the characteristics of malignant B cell clone and do not examine the immune response of the patients.[5]

The major cause of morbidity and mortality in B-CLL is infection-related (due to viral, bacterial or fungal antigens), therefore the extent of the immune defect in B-CLL patients may have a tremendous importance.[2]There is considerable evidence in the literature for a number of qualitative and quantitative T-cell abnormalities in B-CLL. However, it is not clear, if they are a cause or an effect of the disease. Clinical course of CLL patients is highly variable due to dysregulated immune functions. Both subsets of CD4 and CD8 T cells are increased, while the CD4/CD8 ratio is reversed in advanced Rai stages. However, the precise mechanisms that attribute to this immunosuppressive phenotype in CLL in not understood.

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In this study, we analysed the T-cell subset (CD4:CD8 ratio) and correlated with the Rai staging.

MATERIALS AND METHOD

Fifty newly diagnosed cases of CLL were included in the study after taking ethical clearance from institutional ethical committee. This study was conducted over a period of one year. Control samples from20 age and sex-matched individuals of both genderswere collected from apparently healthy individuals at PGIMS Rohtak.

A detailed clinical history and physical examinations were done for all the patientsand classified according to Rai staging system to estimatethe clinical stage. Complete hemogram and cytomorphological analysis was done by examination of Leishman stained peripheral blood smears.(Table 3)

2 ml EDTA peripheral blood immunophenotyping was performed on 8Color Flow cytometer BD FACS Canto II (Becton Dickinson, San Jose, CA). List mode data was acquired and analyzed by FACS Diva software. Expressions of any gated events were plotted on the side scatter (SCC)/CD19 plots and SCC/CD3 plots.

The CD panel used CD45, CD19, CD20, CD23, CD5, CD200, CD38, CD4, CD8, CD3, FMC7, CD10, CD79b, Kappa, Lambda. CD45 is used for gating of lymphocyte populations, and this lymphocytes population was sorted into T and B lymphocyte by using CD3 and CD19. Further CD3 positive population is divided into CD4 and CD8.The number of the CD3, CD4 and CD8 cells was counted and CD4 / CD8 ratio was measured.

RESULTS

There was slight male predominance with male to female ratio of 1.6:1 in our study. Average age of the patients was 60.8 years (range 43-85 years). All 50 CLL patients in the study were categorised by Rai stages (Table 3). Largest numbers of patients were in Rai stage III and IV (n = 26). The mean helper to suppressor ratio (CD4/CD8) of 50 patientswith CLL was 1.2±0.28 as compared to the mean of 20 normal volunteers tested at the same period of time was 1.86 ± 0.64 ($p < 0.00$) (Table 2).

The mean helper to suppressor ratio (CD4/CD8) was normal in 11, equal in 23 and reversed in 16 patients. 24 patients with equal or reversed CD4:CD8 ratio were in Rai stage III/ IV due to a decrease of the absolute number of CD4 + cells.

The absolute numbers of CD4 + and CD8+ cells, as well as the CD4/CD8 ratio according to the different stages of the disease are shown in. Analysis of the data revealed that the decrease of CD4/CD8 ratio observed in stage 0to IV was statistically significant (P value< 0.00) (Table 2). The low CD4/CD8 ratio found in advanced stages is due to a decrease of the absolute number of CD4 + cells (Figure 1, 3)

DISCUSSION

T cells are major components of the adaptive immune system and mature T cells are generally considered to express either the CD4 or CD8 co receptor.[6] CD4 and CD8 are a membrane glycoproteins and membrane of immunoglobulin super gene family.[7]

It is well established that immune dysfunction plays a critical role in CLL development. The progression of CLL is associated with quantitative and qualitative changes in the host's immune system. Interactions between the leukemic cells and the native immune system could be a potentially important influence on disease progression.[12]

These abnormalities include an increase in the absolute number of circulating T cells, impair the cellular immune response, functional defects of helper T cells and low helper to suppressor (CD4/CD8) ratio of T cells.[6,7] The phenotypic feature of both CD4+ and CD8+ cells in B-CLL patients correspond to the antigen-experienced memory and effect or T cell type, but not to the naive T cell type.[8]Both subsets of CD4 and CD8 T cells are increased, while the CD4/CD8 ratio is reversed in advanced Rai stages.[9] Moreover, these cells are oligoclonal, express anti idiotypic determinants specific for the autologous M protein, and display antiplasma cell cytotoxic activity.[10]Nevertheless, the exact mechanism leading to T-cell dysfunction in CLL is not well defined but these patients are prone to increased risk for infections.

In this study, we first conducted a prospective analysis of the number of CD4+ and CD8+ T cells in a group of 50 newly diagnosed CLL patients. Similar to previous results derived from both US and European CLL cohorts, we found that nearly a quarter of CLL patients exhibit inverted CD4/CD8 ratios.[13]

Our study also showed that the correlation of CD4/CD8 ratio with Rai classification the ratio was significantly decreased in patients with CLL in stage III and IV indicating advance form of disease and this agree with previous studies.[13]

The therapeutic modulation of T cell response in these patients may play an important role in the disease behaviour. May be a key event compensating the immunodeficiency characteristic for the advanced stages of the disease.We showed that both the numbers of CD4 and CD8 T cells at diagnosis predict the clinical course of CLL.

CONCLUSION

This study confirms that CD8 expression is a recurrent albeit rare phenomenon in patients with CLL and suggests that CD8 expression has an adverse prognostic impact. CD4/CD8 ratio was decreased in advanced form of chronic lymphocytic leukemia and this simple parameter of immune function seem to have a huge prognostic value for patients with CLL and predict the clinical course of the disease. Therefore, CD8 expression should be further investigated for its potential to contribute to risk stratification in patients with CLL.

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