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T-cell large granular lymphocytic leukaemia in Kashmiri population-A Clinicopathological study at a tertiary care centre

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ABSTRACT

INTRODUCTION: T-cell large granular lymphocytic leukaemia (T-LGL) is a rare clonal hematological disorder characterized by peripheral blood and bone marrow lymphocytic infiltration with large granular lymphocytes (LGLs), splenomegaly, and cytopenia, of which neutropenia is most common . T-LGL is characterized by persistent increase in LGLs ranging from 2×10^9/L to 20×10^9/L on peripheral blood in the absence of a reactive cause . The most common indications for treatment are cytopenia, recurrent infection, pure red cell aplasia, progressive splenomegaly, and B symptoms.

AIM OF THIS STUDY: This study was carried to study the clinicopathological parameters of LGL in Kashmiri population . It is an unusual lymphoproliferative neoplasm with a high index of suspicion needed for its diagnosis

MATERIAL AND METHODS: This study was conducted in the department of Hematology, Sher e Kashmir institute of Medical Sciences for a period of 3 years from 2014 to 2017.During this duration, we received 6 cases of LGL leukaemia. Clinical data of the patients was collected in terms of age, clinical symptoms, baseline investigations, bone marrow examination, flowcytometry and treatment received. The data was analysed using SPSS 16.0 software.

RESULTS: This study was carried over a period of 3 years in which we came across 6 cases of LGL. They included 3 males and 3 females. The age of the patients ranged from 9 years to 65 years. Mean age of patients was 42.5 years. The most common presentation in our study was persistent lymphocytosis.

CONCLUSION: LGLS have a very low incidence. However, It remains unclear if the incidence is truly low or the disease has been underdiagnosed because most cases are asymptomatic on presentation. This raises the importance of reviewing the peripheral smears in asymptomatic patients who have persistent lymphocytosis or neutropenia. Systematic long-term follow-up studies need to be performed.

Keywords: NIL.

INTRODUCTION

T-cell large granular lymphocytic leukemia (T-LGL) is a rare clonal hematological disorder characterized by peripheral blood and bone marrow lymphocytic infiltration with large granular lymphocytes (LGLs), splenomegaly, and cytopenia, of which neutropenia is most common .[1] T-LGL is characterized by persistent increases in LGLs ranging from 2×10^9/L to 20×10^9/L on peripheral blood in the absence of a reactive cause.[2]

The World Health Organization (WHO) classification has recognized LGL leukemia as a specific entity among mature peripheral T-cell neoplasms, including $CD3^+$ T-cell LGL (T-LGL) and $CD3^-$ natural killer (NK)-LGL leukemia subtypes.[3]

T-LGL leukemia has a $CD3^+/CD8^+/CD45RA^+/CD57^+/CD62L$ negative phenotype compatible with a terminal effector

memory T-cell expansion due to antigen-driven T-cell activation, along with increased cell survival. A T-cell receptor (TCR)-β/γ rearrangement underlines the monoclonal nature of the T-LGL expansion. NK-LGL leukemias include chronic NK-LGL lymphocytosis, usually an indolent disease, and aggressive NK-LGL leukemia.

T-LGL typically presents in the sixth decade of life, with an equal male to female ratio .4 Approximately one third of patients are asymptomatic when routine blood counts reveal cytopenia and LGL, which leads to diagnosis. The symptoms, if present, are related to cytopenia .5 Bone marrow aspirate may be required to confirm the diagnosis, especially in those with low absolute numbers of circulating LGLs. Patients with T-LGL have a median survival of more than 10 years .6 The most common indications for treatment are cytopenia, recurrent infection, pure red cell aplasia, progressive splenomegaly, and B symptoms.7

MATERIAL AND METHODS: This study was conducted in the department of hematology, Sher e Kashmir institute of Medical Sciences for a period of 3 years from 2014 to 2017.During this duration,we received 6 cases of Large Granular Lymphocytic leukaemia(LGL). Clinical data of the patients was collected in terms of age, clinical symptoms, baseline investigations, bone marrow examination, flowcytometry and treatment received.

AIM OF THIS STUDY: This study was carried to study the clinicopathological parameters of LGL in Kashmiri population. It is an unusual lymphoproliferative neoplasm with a high index of suspicion needed for its diagnosis

RESULTS: We present a series of 6 cases studied during a period of 3 years.

Case 1: 9 years old boy presented with generalized weakness for 2 Months and Breathlessness for 15 days with past history of frequent chest infections. On Clinical Examination, pallor was seen. Spleen was palpable 4cm Beyond Costal Margin (BCM) with Hepatomegaly 2cm BCM. Systolic murmur was present at apex. Chest/CNS examination was normal. CBC showed Haemoglobin of 2.07 g/dl ,MCV of 89 fl , TLC of 10.2x103/mm3.Absolute neutrophil count was 400/mm3. Platelets were 179 x103 /mm3 PBF showed many activated lymphocytes (50%). KFT/ LFT/ Coagulogram was Normal .HbsAg / Anti-HCV/ HIV /Rheumatoid Factor /Anti Nuclear Antibody were Negative.Direct Coombs Test/Indirect Coombs Test were Negative.USG showed Mild Hepatosplenomegaly . Echocardiography showed Normal study. Quantitative immunoglobulin levels were normal. Bone Marrow aspiration showed Hypocellular marrow with erythroid hypoplasia, eosinophilia (10%) and increased iron stores. BM Trephine biopsy also showed Hypocellular marrow with marked erythroid hypoplasia, lymphocytosis with increase in eosinophils. Subsequently patient was treated with steroids for Pure Red Cell Aplasia (PRCA), in addition to transfusion support. As patient was transfusion dependent despite being on steroids splenectomy was performed. Histopathological examination of Spleen showed congestion of red pulp with scattered foci of extra medullary haemopoeisis within sinusoids.Despite splenectomy patient remained transfusion dependent. Patient was reviewed and in view of PRCA , neutropenia and indolent course, flow cytometry of peripheral blood was performed. On flowcytometry, diagnosis of LGL Leukemia was made. Patient was put on Methotrexate 10 mg weekly. Developed drug induced hepatitis with methotrexate. Patient was shifted to Cyclophosphamide but continued to be transfusion dependent. So patient was started on cyclosporine 4mg/m2 /day .Patient responded and became transfusion independent with Heamoglobin rising from 3.5g/dl to 10.5g/dl with reversal of lymphocytosis.

CASE 2 : 44 years female presented with generalized weakness. Examination revealed pallor with cervical lymphadenopathy and no organomegaly. CBC showed Hb of 8.0 g/dl , TLC of 12.03x103/mm3, Platelets of 282x103/mm3 with ANC of 3729/mm3. On PBF,71% Atypical lymphocytes were seen.KFT/LFT/Viral serology was Normal .DCT/ICT/RF/ANA were Negative. CXR/USG was Normal.Flow cytometry showed CD2+, CD3+, CD5+, CD7+, CD8+, CD4-, CD56+, ZAP70+ making a diagnosis of T- LGL. Patient was Started on Methotrexate 10mg weekly orally. However there was no response. Subequently MTX 10mg / week and Cyclophosphamide 50 mg twice /week were started.Repeat CBC showed Hb of 12.7 g/dl, TLC of 17.6x103/mm3, Platelet of 203x103/mm3. After 12 months of MTX 10

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mg/week and Cyclophosphamide 50 mg/day, CBC showed Hb of 14 g/dl, TLC of 18.5x103, Platelet count of 220x103/mm3.Repeat CBC After 20 months showed Hb of 13.7g/dl, TLC of 11.7x103/mm3,and Platelet count of 165x103/mm3.

Case 3 : 65 years hypertensive male on Amlodipine presented with anemia . No LAP or Organomegaly was present.CBC showed Hb of 5.7g/dl, TLC of 15.75x103/mm3, Platelet count of 340 x103/mm3 and Absolute Neutrophil Count of 1400/mm3. PBF showed 90% mature lymphocytes.KFT / LFT / Viral serology was Normal. DCT was positive, ICT was negative. Serum LDH / Haptoglobin levels were Normal. RF / ANA / viral serology was Negative.Iron profile normal .CXR / USG / Echo were Normal .Flow cytometry showed Bright positivity for CD 45, Moderate positivity for CD2, CD7, CD3, CD57, CD8 and Dim positivity for CD43, CD5, TCR A/B.Diagnosis of LGL was made on flowcytometry. Cytogenetics was Normal. Patient was given Prednisolone 20mg daily and Methotrexate 10mg weekly. After 6 months,CBC showed Hb of 10.9g/dl, TLC of 12.3 x103/mm3, Platelet count of 264 x103/mm3 .PBF showed lymohocytosis(73%)Prednisolone was stopped and patient was kept on weekly methotrexate.

Case 4 : 50 years female presented with symptomatic anemia and decreased appetite .Clinically she had pallor and no organomegaly.CBC showed Hb of 6.9g/dl, TLC of 12.5x103/mm3, Platelet count of 299x103/mm3 with of ANC- 1000/mm3.PBF showed Atypical lymphocytes(60%), with granules.KFT / LFT/ Viral serology was Normal.RF/ ANA/ viral serology were Negative.Chest X Ray / USG was Normal.DCT/ICT were Negative.On BM aspiration and BM biopsy diagnosis of CLPD was made. Cytogenetics were Normal .Flow cytometry showed Bright positive CD2, CD3,CD5 and CD7 and Negative for B cell and myeloid markers. There was CD4/CD8 reversal .Patient was Started on cyclophosphamide 50mg /day.After 6 months,CBC showed Hb of 12.6 g/dl , TLC of 4.04x103/mm3, Platelet count of 226x103/mm3 .

Case 5: 42 years hypertensive,diabetic,hypothyroid male presented with generalized weakness.CBC showed Hb of 13.1 g/dl , Platelets of 2,37,000/µl and TLC of 19,400/µl with differential count of Neutrophils 24%, lymphocytes 65%, monocytes 09% and eosinophils 02%(Figure 1). All other investigations including viral serology were normal .Flowcytometry showed positivity for CD2,CD3, CD5,CD 7, CD25,CD57 and negative for CD64 and CD 16(Figure 2). Diagnosis of LGL leukaemia was made.

Case 6 : 45 years old Hypothyroid female presented with Left Hypochondrium pain and easy fatigability for 20 days.On examination, cervical & Axillary LAP was seen with massive splenomegaly .Investigations revealed mild pancytopenia with high LDH.PBF showed few atypical cells .BM examination showed 13% abnormal cells suggestive of NHL. Histopathological examination of Rectal biopsy showed NHL infiltration. Flow cytometry was inconclusive. Immunohistochemistry of Lymph node was done and a diagnosis of NK / T Lymphoma was made. Patient Received 3 cycles of SMILE regimen. Interim CT after 2 cycles of chemo showed marked response

Discussion:

This case series demonstrates the clinicopathological features of LGL. This study was carried over a period of 3 years in which 6 cases of LGL were studied and kept on a close follow up..They included 3 males and 3 females. Mean age of patients was 42.5 years. In a study conducted by Rashid A et al 8 , median age at presentation was 61 years and among 4 cases taken in the study , 1 was female. 40% cases of LGL are asymptomatic and are discovered incidentally through persistent neutropenia, asymptomatic lymphocytosis, or as an associated phenomenon with autoimmune disorders such as RA. Peripheral smear examination is very helpful in such cases. 8The most common presentation in our study was persistent lymphocytosis. Persistent lymphocytosis was seen in studies carried out by Rashid A et al8 and Kondoh K et al 9 In our case series ,case 1 had several interesting features. The 9 years old boy presented with symptomatic anemia with Past H/O frequent chest infections. CBC showed Absolute neutrophil count of 400/mm3 . Platelets were 179 x103/mm3. PBF showed Many activated lymphocytes(50%). BM aspiration showed Hypocellular marrow with erythroid hypoplasia, eosinophilia (10%)and abundant iron stores. BM Trephine biopsy also showed Hypocellular marrow with marked erythroid hypoplasia, lymphocytosis with increase in

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eosinophils. Subsequently patient was treated with steroids for Pure Red Cell Aplasia (PRCA), in addition to transfusion support. As patient was transfusion dependent despite being on steroids splenectomy was performed.. Despite splenectomy patient remained transfusion dependent. Patient was reviewed and in view of PRCA , neutropenia and indolent course, Subsequently flow cytometry of peripheral blood was performed. On flowcytometry, diagnosis of LGL Leukemia was made. Patient was put on Methotrexate 10 mg weekly. Developed drug induced hepatitis with methotrexate. Patient was shifted to Cyclophosphamide but continued to be transfusion dependent. So patient was started on cyclosporine 4mg/m2 /day .Patient responded and became transfusion independent with Heamoglobin rising from 3.5g/dl to 10.5 g/dl with reversal of lymphocytosis. Most bone marrow specimens from the T-cell LGL patients contain interstitially distributed clusters of at least CD8+ or TIA-1+ lymphocytes or clusters of at least granzyme B+ lymphocytes, or granzyme B+. Cells from patients with LGL leukemia usually contain acid phosphatase and â-glucuronidase. T-LGL cells express the pan T-cell antigens CD2, CD3 and CD5 and the suppressor T-cell associated antigen CD8. They usually express NK-cell associated antigens such as CD16 (FC receptor for IgG), CD56 and CD57. Clonal rearrangement of the Tcell receptor has been reported10,11. Few reports have been made of cytogenetic analysis in patients with this disorder. Chromosomal abnormalities are often not detected, when detected there are no consistent abnormalities. Trisomies 8 and 14, 6q- , and inv (14) have been reported. The most frequent structural abnormality appears to be deletion of 6q with two cases of del(6)(q21) and 1 case of del(6)(q21q25) reported as part of complex karyotypic aberrations, and 2 cases of del(6)(q21q26) as the sole chromosomal abnormality.12 As far the treatment is concerned, Currently, there is no standard treatment for patients with T-LGL. For asymptomatic T-LGL patients with an indolent course, a wait-and-see approach can be considered .13

CONCLUSION: LGLS have a very low incidence. However, It remains unclear if the incidence is truly low or the disease has been underdiagnosed because most cases are asymptomatic on presentation. This raises the importance of reviewing the peripheral smears in asymptomatic patients who have persistent lymphocytosis or neutropenia. Systematic long-term follow-up studies need to be performed.

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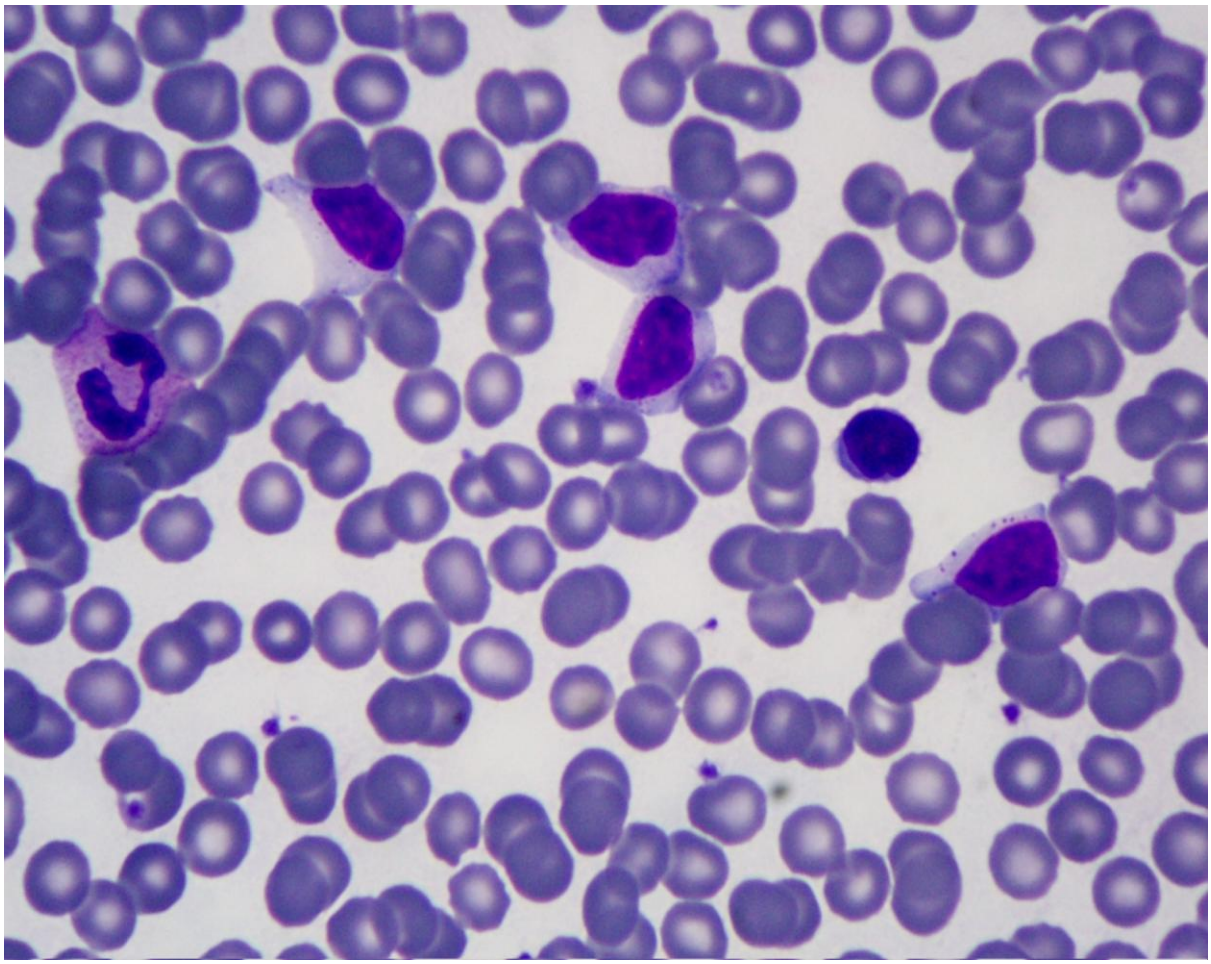
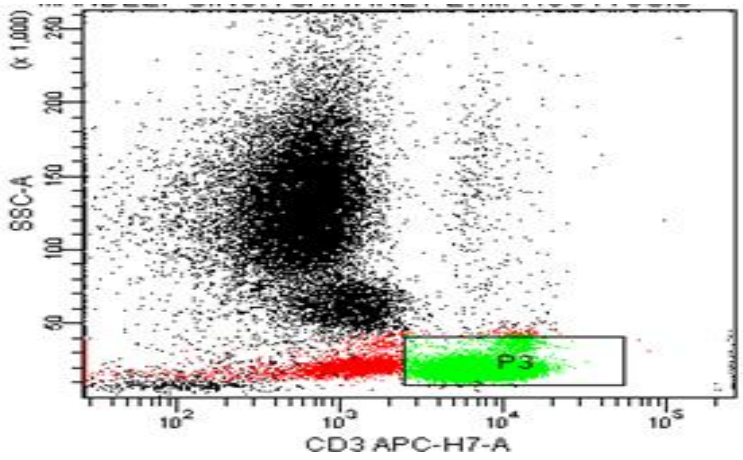


Figure 1: Photomicrograph of Peripheral blood film showing atypical granular lymphocytes(Leishmann stain,40X)



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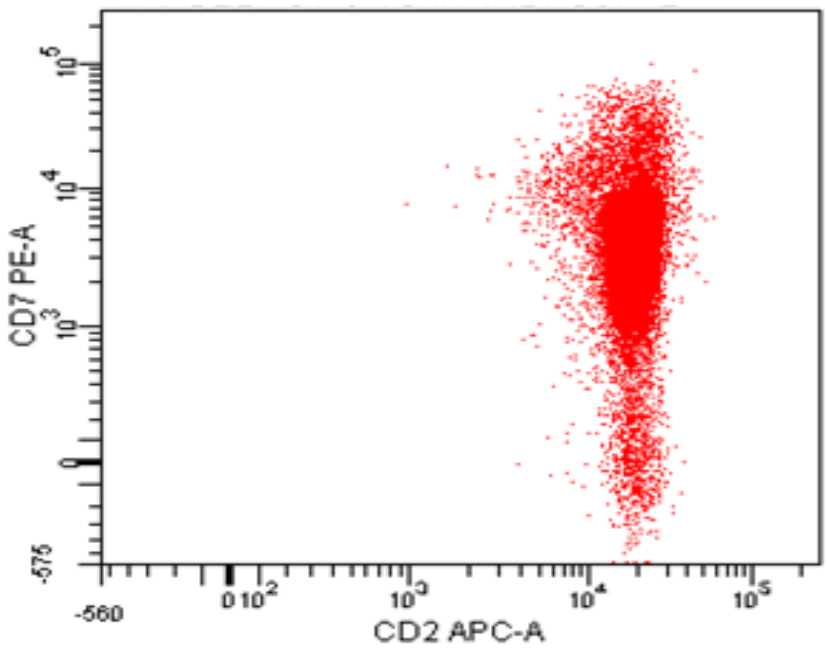

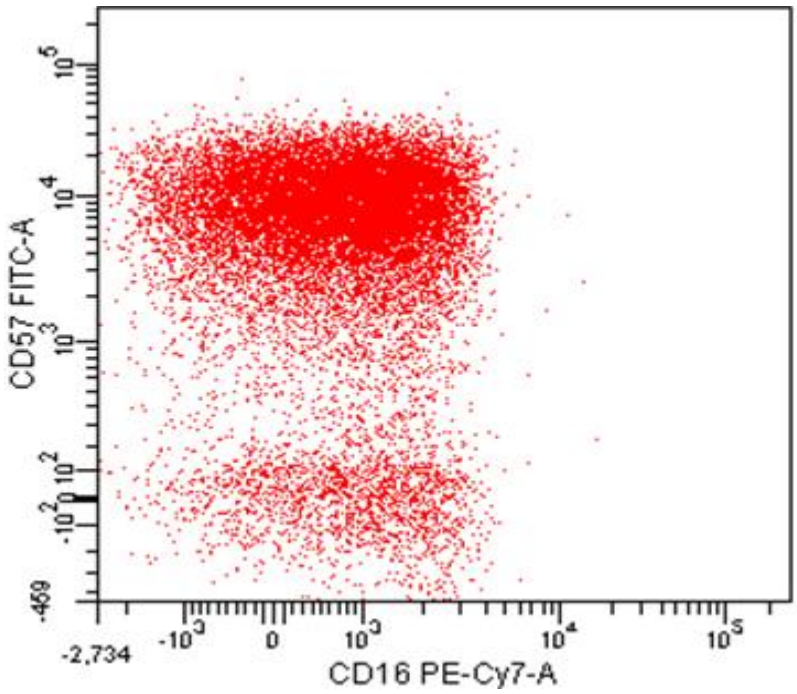

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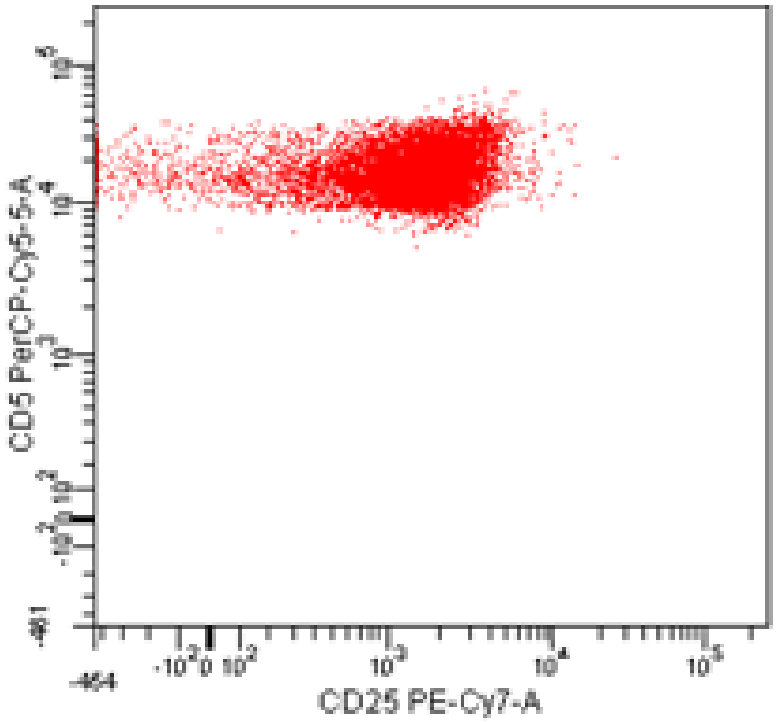

Figure 2: Flowcytometry graphs showing positive CD2, CD3, CD5,CD 7, CD25,CD57 and negative CD64 and CD 16 markers

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