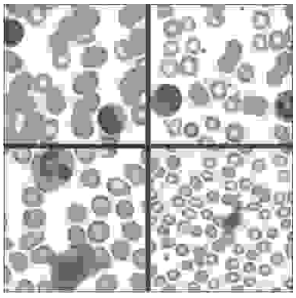
CASE REPORT PROF-1270

REACTIVE LYMPHOCYTOSIS;
AN ENIGMA OF DIAGNOSIS.



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ABSTRACT... bugsgallian@yahoo.com A case of reactive lymphocytosis is described who despite all the relevant investigations and clinical evaluation eluded a conclusive diagnosis.

Key words: Persistent lymphocytosis, reactive lymphocytes

INTRODUCTION

In adults the absolute lymphocyte count is $4x10^9$/L. Lymhocytosis may be primary i.e. due to an intrinsic defect in the lymphocyte population or secondary (Reactive). Reactive lymhocytosis in adults is primarily due to physiologic or path physiologic response to infection, toxins, cytokines or unknown factors. If reactive lymphocytosis persists then its diagnosis requires a thorough clinical examination with all the pertinent lab investigations. The initial concern of the treating physician for such a patient is that whether the lymphocytosis is monoclonal or polyclonal in its origin. Further concerns are regarding the lineage of the lymphocytes. With the present day diagnostics it is seldom that a diagnosis can be missed. Here we report an interesting case of reactive lymhocytosis which despite all the relevant investigations and clinical reviews eluded a conclusive diagnosis.

CASE REPORT

A twenty seven years old male presented with complaints of generalized weakness and easy fatigability for the past one month (2007). The past history of the individual deserves a special mention here. The patient presented for the first time with the history of evening rise of temperature, productive cough and generalized weakness of two weeks duration (2002).On examination he was found to have an absolute lymphocytosis with 90% lymphocytes in the peripheral blood. He had a raised ESR of 98 mm fall in the first hour by Westergrens method. Morphologically the lymphocytes appeared to be reactive. On X- ray chest he had hilar and perihilar opacities in the left lung. He was empirically put on anti tuberculosis regimen (ATT).The patient became afebrile after three weeks of starting the medication. He remained asymptomatic till the year 2006 when he again reported to a hospital in the northern areas near his place of duty. He this time presented with occasional fever and easy fatigability. He was investigated on the lines of relapsed pulmonary tuberculosis. His X- ray chest showed that he still had hilar and perihilar opacities in the left lung. He had a raised ESR of 130 mm fall in the first hour by Westergrens method. His sputum was negative for acid fast bacilli. An absolute lymphocytosis with a lymphocyte count of more than $4x10/^9$ l in the peripheral blood was seen. He had 92% lymphocytes in the peripheral blood

while morphology was suggestive of activated lymphocytes.

The patient was transferred to a tertiary care hospital to rule out the possibility of reactivated pulmonary tuberculosis, to identify the nature of lesion in the lungs and to identify the cause of persistent lymphocytosis. He had HRCT of the lungs which revealed the lesion of the left lung to be early bronchiectic changes with consolidation. Repeated analysis of bronchi alveolar lavage/was negative for acid fast bacilli.Histopathological examination of an enlarged/ left supraclavicular node showed reactive hyperplasia. Sputum examination for acid fast bacilli was negative. On the basis of clinical examination and investigations the possibility of patient suffering from relapsed pulmonary tuberculosis was ruled out. Attention was then focused to find out the nature and cause of persistent lymhocytosis.

Bone marrow aspiration and biopsy were performed. The aspirate showed reactive lymphocytosis with 92% lymphocytes in the marrow. Bone marrow biopsy was suggestive of an abnormal lymphoid infiltrate. Flow cytometery was performed to rule out malignant nature of disease. Flow cytometery of the peripheral blood showed a polyclonal lymphoctosis. Pan T cell marker (CD3+) was present in more than 93% of lymphocytes. Expression of HLA DR was increased while expression of CD7+ lymphocytes was decreased. The findings were suggestive of mononuclear lymphocytosis probably secondary to a viral infection. Serology for EBV, CMV, Hepatitis viruses and HIV was suggested.

Infectious mononucleosis leads to Pan-T lymphocytosis.Monospot test for heterophile antibody and IgM to EBV was negative. Similarly Complement fixation tests for CMV serology (IgG = I/20) was negative. There was no evidence of Hepatitis B and C infection. Serology for HIV viral infection was negative. Dengue IgM and investigations for malarial infection were also negative.

Liver function tests and lactic dehyrogenase (LD) levels were normal. The CRP levels were serially monitored but were not raised.

The patient occasionally complains of fatigue and generalized weakness. Other causes of reactive persistent lymphocytosis were not deemed fit to be investigated as those did not match with the clinical picture of the patient. He still has an absolute lymphocyte count of $7.810x^{9}$/ 1itre with 94% lymphocytes in the peripheral blood. He is on no medication since last one year and is being regularly reviewed clinically and monitored for his counts every month but still eludes a diagnosis.

DISCUSSION

Reactive lymhocytosis can be due to mononucleosis syndrome[1] .The syndrome can be caused by infection of EBV, CMV and infection by Toxoplasma gondii. Infections due to HIV, HSV type II, Varicella-zoster virus, Rubella virus, Bordetella pertussis and adenovirus can also cause reactive lymhocytosis[2]. Persistent lymphocytosis can be caused by malignancies, chronic inflammatory diseases, autoimmune conditions and hypersensitivity reactions.

The approach of the treating doctor in cases of reactive and persistent lymphocytosis is influenced and directed by the patient's history, clinical examination and investigations. The main concern for such patients is the exclusion of acute and chronic lymphocytic leukemia[3]. However in children and young adults lymphocytosis is almost always reactive, due to infections[4].The clinical algorhythm of elaborate clinical history, examination and pertinent investigations ruled out the possibility of reactivated pulmonary tuberculosis from the very beginning. With the clinical history and the physical findings of our patient it was very likely that the lymphocytosis was viral in origin. The bone marrow findings and flow cytometeric analysis of the peripheral blood suggested that reactive lymphocytosis was very likely due a viral insult[5]. Three viruses are particularly prone to cause marked lymphocytosis eg EBV, CMV and Hepatitis viruses[6]. The typical morphology of the lymphocytes i.e. large with abundant blue cytoplasm having enlarged nuclei with fine chromatin and prominent nucleoli with an increased lymphocyte count are typical for viral infections. The flow cytometery showed T cell lymphocytes with an increased CD3+ count which

pointed towards the possibility of Infectious Mononucleosis[7].

However the extensive viral serology yielded different results. Bordetella infection was ruled out on the basis of history and clinical examination. The typical morphology of the lymphocytes was absent for the condition and the nasopharyngeal swabs were negative for culture. Similarly the history and examination ruled out the possibility of Toxoplasmosis[8]. At this juncture it was decided that one last ditch consolidated effort be made to identify the intriguing cause of lymphocytosis. The patient was then investigated to rule out any possibility however remote of entities like solid tumors, Thymoma, Sarcoidosis, Wegener granulomatosis, Rheumatoid arthritis and possible hypersensitivity reactions[9]. No evidence of any afore mentioned pathologies was present. The next logical step was taken in this regard. As the patient did not have any other symptoms except easy fatigability it was suggested to observe the patient for a few weeks or months[10]. If the patient becomes symptomatic, or has significant lymphadenopathy or splenomegaly, or has significant anaemia, thrombocytopenia, or neutropenia, then further evaluation including flow cytometery be performed more quickly[11].

REFERENCES

1. Zambello R, Semenzato G. **Large Granular lymphocytosis.** Haematologica. 1998; 83(10): 936-42.

2. Gahler A, Cogliattis S, Korte W. **Differential diagnosis of absolute lymphocytosis.** Ther Umsch.2004; 33:196-207.

3. Brychtova Y, Doubek M. **Lymhocytosis with large granular lymphocytosis: case report.** Vnitr Lek.2000; 46(5):301-4.

4. Wolf G, Shulz H. **Reactive polyclonal T cell lymphocytosis mimicking Sezary syndrome in patient with Hairy cell leukemia.** Haematologica.2001; 86(10): 27.

5. Furust S. **Leukocytosis as an incidental finding.** Fortschr Med.2001; 43(17):33-7.

6. Krober SM, Horny HP, Greshnoik A. **Reactive and neoplastic lymphocytosis in human bone marrow morphological, immunological and molecular biological investigations in biopsy specimens.** Clin Path 1999; 52(7):521-6.

7. Ren Y, Medeiros LJ, Amin HM. **Unusual expression of CD94 on CD8+ TCR alpha-beta T-cells in Infectious mononucleosis.** Ann Diag Pathol. 2007; 11:55-68.

8. Khan S, Myers K. **Persistence of natural killer cells (NK) lymphocytosis with hyposplenism without development of leukemia.** Clin Pathol. 2005; 7:5-8.

9. Tokura Y, Matsuoka H, Koga C. **Enhanced T-cell response to mosquito extracts by NK cells in hypersensitivity to mosquito bites associated with EBV infection and NK cell lymphocytosis.** Cancer Sci 2005. 96;5:19-26.

10. Just-Nubling G, Korn S, Ludwig B, Stephen C. **Primary Cytomegalovirus infection in an out patient setting laboratory markers and clinical aspects.** Infection.2003; 31 (5):318-23.

11. Stiger D. **Ciprofloxacin induced acute interstitial pneumonitis.** Eur Respir J.2004 ;(1): 172-4.