CD4 Lymphocytopenia without HIV Infection

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Abstract: It is well known that the most common cause of the low CD4 (CD4 less than 300/mm^3) is the long term HIV infection. Other far less common causes include tuberculous infection, lymphoma, etc. The aim of this report is to describe the low CD4 count in various diseases, except for HIV infection. **Patients and Methods:** This cross-sectional study recruited the IPD medical patients who had lymphocyte < 1,000/mm^3 during 1 Jan-31 Mar 2015. They would be checked for CD4 using the flow cytometry method, BD FACSCalibur$^®$ and only ones who had CD4 ≤250/mm^3 without HIV infection, aplastic anemia, myelodysplastic syndrome, leukemia, steroid, chemotherapy or radiotherapy and organ transplantation were collected for demographic and clinical data study and expressed as the percentage, mean and standard deviation. **Results:** From 14 patients with lymphocyte < 1,000/mm^3, only 10 patients had CD4 < 250/mm^3, consisting of 8 males and 2 females, their ages ranged from 22 to 85, mean 53.7±23.7 years. Four patients were older than 60 years. Their active diseases were pneumonia with respiratory failure (3 cases), COPD with respiratory failure (2 cases), pulmonary tuberculosis (2 cases), disseminated tuberculosis, adult onset Still's disease and lepromatous leprosy (1 case for each). The mean for lymphocyte, T cell and CD4 count were 475.3±175.6, 323.9±179.9 and 158.9±62.2/mm^3, respectively. **Conclusion:** Low CD4 count can be occasionally found in various diseases such as severe pneumonia, tuberculosis. It may contribute the patients to be vulnerable to opportunistic and more serious infections.

Key Words: CD4 Lymphocytopenia, No HIV Infection

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บทคัดย่อ: **ภาวะเซลล์ CD4 ต่ำโดยไม่มีการติดเชื้อเอชไอวี**

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**นักศึกษาแพทย์, มหาวิทยาลัยแพทยศาสตร์จีน, เมืองเสิ่นหยาง, สาธารณรัฐประชาชนจีน

เป็นที่รู้กันทั่วว่าสาเหตุที่ทำให้ CD4 lymphocyte ต่ำ (CD4 <300/mm^3) ที่พบบ่อยที่สุดคือการติดเชื้อ HIV เป็นเวลานาน ส่วนน้อยมาก ๆ ที่อาจจะพบในภาวะอื่น ๆ ได้ด้วย เช่นติดเชื้อวัณโรค, มะเร็งต่อมน้ำเหลือง วัตถุประสงค์ของการศึกษานี้คือศึกษาค่า CD4 ต่ำในโรคอื่น ๆ นอกเหนือจากการติดเชื้อ HIV **ผู้ป่วยและวิธีการ:** เป็นการศึกษาภาคตัดขวางระหว่าง 1 มกราคม-30 เมษายน 2558 ผู้ป่วยในของกลุ่มงานอายุรกรรมที่มี lymphocyte < 1,000/mm^3 จะได้รับการตรวจ CD4 ด้วยวิธี flow cytometry, BD FACSCalibur$^®$, รวบรวมเฉพาะผู้ป่วยที่ CD4 เท่ากับ หรือ < 250/mm^3 โดยที่ผู้ป่วยต้องไม่มีการติดเชื้อ HIV, ไขกระดูกฝ่อ, myelodysplastic syndrome, มะเร็ง เม็ดเลือดขาว, ไม่ได้รับยาเคมีบำบัด/สเตอรอยด์, รังสีรักษา และไม่มีการเปลี่ยนถ่ายอวัยวะ รวบรวมข้อมูลพื้นฐาน และข้อมูลทางคลินิกแสดงเป็นร้อยค่าตัวกลางเลขคณิตและค่าเบี่ยงเบนมาตรฐาน **ผลการศึกษา:** จากผู้ป่วย 14 รายที่มี lymphocyte < 1,000/mm^3 มี 10 รายที่มี CD4 < 250/mm^3 เป็นชาย 8 รายหญิง 2 รายอายุ 22 ถึง 85, เฉลี่ย 53.7±23.7 ปี มีผู้ที่อายุเกิน 60 ปี 4 ราย เป็นผู้ป่วยปอดบวมร่วมกับภาวะหายใจวาย 3 ราย ถุงลมโป่งพองร่วมกับ ภาวะหายใจวาย 2 ราย วัณโรคปอด 2 ราย วัณโรคกระจาย 1 ราย Still's disease ที่อาการเริ่มในวัยผู้ใหญ่ 1 ราย และ โรคเรื้อนรุนแรง 1 ราย ค่าเฉลี่ย lymphocyte, T cell และ CD4 คือ 475.3±175.6, 323.9±179.9 และ 158.9±62.2/ mm^3, ตามลำดับ **สรุป:** CD4 ต่ำพบได้เป็นบางครั้งในภาวะหลากหลายเช่นปอดบวมแบบรุนแรง วัณโรคอาจทำให้ ผู้ป่วยเสี่ยงต่อการติดเชื้อฉวยโอกาส ที่รุนแรงยิ่งขึ้นเพิ่มได้

คำสำคัญ: CD4 Lymphocytopenia, ไม่มีการติดเชื้อเอชไอวี

Introduction

The CD4 lymphocyte or the helper T cell is an important part of the immune system. Its important role is to facilitate and to help B lymphocyte to produce antibody specific to the stimulating antigen. In the normal peripheral blood, its median count is 890/mm^3, ranging from 359 to 1,954/mm$^{3[1]}$ whereas mean CD4 among healthy Thais is found to be 910±300/mm$^{3[2]}$. It is the main target of HIV infection, the longer duration of infection, the lower CD4 level until the CD4 count is used to be the starting point of antiretroviral therapy in cases of HIV infection[3].

The individuals who have the CD4 count lowered than 250-300/mm^3, are defined as CD4 lymphocy-topenia and they are risky to numerous opportunistic infections[4]. The cause of CD4 lymphocytopenia in almost all cases is HIV infection however other causes in the minority may include few cases of tuberculosis, SLE, Sjogren's syndrome, lymphoma, aplastic anemia, myelodysplastic syndrome, corticosteroid or other immunosuppressant usage, sarcoidosis, X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN) syndrome[5,6] and idiopathic CD4 lymphocytopenia[7].

The purpose of this paper is to describe the patients who are admitted due to various active diseases and accidentally found to have CD4 lymphocytopenia.

Patients and Methods

This cross-sectional study recruited the patients who were admitted in the medical wards, Maharat Nakhon Ratchasima Hospital due to various active diseases during the period, 1st Jan 2015-31st Mar 2015. All patients were routinely investigated with complete blood count using the automate analyzer and other appropriate laboratory tests depending on the main active diseases. If they had total lymphocyte count less than 1,000/mm^3, their CD4 counts from the venous blood sample would be further studied, using the flow cytometry method, BD FACSCalibur$^®$. Only patients who had CD4 lymphocyte of 250/mm^3 or less, would be recruited into our study. They would be further checked for liver, kidney function tests, cholesterol, albumin, globulin, and the chest radiograph. The exclusion criteria included pregnancy, positive anti-HIV antibody or HIV antigen, aplastic anemia, myelodysplastic syndrome, acute or chronic leukemia, on chemotherapy/corticosteroid/other immunosuppressants, organ transplantation or during radiotherapy.

Their demographic and clinical data would be collected, described and expressed as the percentage, means and the standard deviations.

Results

There were 14 patients having total lymphocyte count less than 1,000/mm^3, only 10 patients met the inclusion criteria, 8 males and 2 females. Their ages ranged from 22 to 85, mean 53.7$\pm$23.7years and four of them were more than 60 years old. No one had history of blood transfusion, homosexuality, or intravenous drug abuse. Only one man was a prisoner and another man had an HIV-infected wife under the antiretroviral therapy. Their main active diagnoses were shown in the table 1.

Among them, no one had oral moniliasis, pruritic papular eruption or ground glass appearance on the chest films. All three patients with pneumonia were more than 60 years old and every one had bilateral diffuse alveolar infiltration on the chest films. All were treated with many antibiotics and oseltamivir but they all passed away due to respiratory failure within 1-2 weeks after admission. For two cases with pulmonary tuberculosis, they both had pleural effusion, one side in the one patient and two sides in the other. One disseminated tuberculosis patient had pulmonary tuberculosis with tuberculous meningitis. Their demographic data, white blood cells, T cells and the CD4 count were shown in the table 2.

The means and standard deviations of the WBC, total lymphocyte, absolute T cell and absolute CD4 counts were 12,550$\pm$6,533.5/mm^3, 475.3$\pm$175.6/mm^3, 323.9$\pm$179.9/mm^3 and 158.9$\pm$62.2/mm^3,

Table 1 The main active diseases of the patients who had low CD4 count without HIV infection

Pneumonia with respiratory failure	3
COPD with respiratory failure	2
Pulmonary tuberculosis	2
Disseminated tuberculosis	1
Adult onset Still's disease	1
Lepromatous leprosy	1

Table 2 The demographic data, the white blood cells, the total lymphocytes, T cells and CD4 count of all 10 patients.

Sex	age	WBC	total lymphocyte	T cell	CD4
F	82	14,400	432	138	109
M	38	13,400	542	385	250
M	29	10,900	736	405	97
F	22	7,900	695	246	135
M	44	5,100	332	367	250
M	32	8,800	484	328	176
M	76	6,000	648	753	201
M	85	18,000	252	257	153
M	72	27,100	271	115	63
M	57	13,900	361	245	155

respectively. No one had leukopenia, absolute neutropenia or thrombocytopenia.

And the means±standard deviations of other blood tests included: serum creatinine 0.84±0.39 mg%, two of them having creatinine >1.50 mg%, albumin 2.8±0.5g%, globulin 3.6±0.7g%, and cholesterol 144.9±28.4 mg%, two of them having total cholesterol <120 mg%.

Discussion

Among 14 patients with total lymphocyte count <1,000/mm^3 during the study period, 10 patients (71.4%) have CD4 count of 250/mm^3 or less. Ashir et al demonstrate that the total lymphocyte count correlates well with CD4 count, r = 0.68 (p=0.001)[8]. However, the CD4 lymphocyte count can vary by 13% when it is measured 4 weeks apart and the physiologic variance may account for 85% of all variance, and by 25% if it is measured 8 weeks apart[9].

Furthermore, the normal CD4 count is quite different among the different ethnic background, the study of the normal black people in Senegal shows that 12.6% have CD4 < 500/mm^3, 6.5% CD4 < 350/mm^3, 1.9% CD4 < 200/mm$^{3[10]}$. Likewise, the range of CD4 count is found to be 343.6-1,493.2/mm^3 in Kenya, 312.2-1,367.6/mm^3 in Tanzania, 265-1,932/mm^3 in Ghana, 490-1,640/mm^3 in Germany, 490-1,670/mm^3 in Italy, 310-1,140/mm^3 in Switzerland[11]. For Asian population, it is found to be 252-2,082/mm^3 in China[12].

Our cases are found to have low CD4 count during admission associated with various active diseases and the study of the CD4 count is not repeated to see whether it is still low or becomes normal after the victims recover from their active main illnesses therefore the conclusion cannot be made whether our patients have prior low CD4 until they are vulnerable to various infections or the low CD4 is resulted from such various active diseases. Likewise, the diagnosis of idiopathic CD4 lymphocyto-penia (ICL) cannot be established because it needs to repeat the study of CD4 and it must be <300/mm^3 for 2 times six weeks apart and the patients must not have any other causes of immunodeficiency[13].

The low CD4 in 4 cases may be associated with their aging because they are older than 60 years with the averaged serum albumin less than usual. Because the absolute CD4 as well as CD8 lymphocytopenia can be found in the individuals with 61-87 years of age with either marasmus or kwashiorkor without HIV infection[14].

One patient has disseminated tuberculosis (TB) which can be one of possible causes of profound CD4 lymphocytopenia[15],viz., 14% of patients with

ad-vanced, disseminated TB presented with CD4 cells below 300/mm^3 in the absence of HIV infection[16]. When these patients are adequately treated with multiple antituberculous drugs, the CD4 becomes normal itself[17]. On the other hand, the patients with pre-existing CD4 lymphocytopenia may also be at increased risk for TB.

The fate of CD4 count is not similar in different entities, in HIV-infected patients without antiretroviral therapy, it would be gradually decreased but it can be restored after treatment. But it is low and persistent in ICL. On contrary, the low CD4 count found in other diseases is usually transient[18]. The further CD4 count study should be performed again in non-HIV infected patients to separate ICL from other entities.

There have been reports of rare cases who have markedly decreased CD4 count due to HIV infec-tion[19,20] but the anti-HIV antibody cannot be detected. Only HIV antigen and high viral load are demonstrated in the patients with repeated opportunistic infections. However, our cases are tested and found negative for HIV antigen as well as HIV antibody.

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