Improvementof Aplastic Anemia and HIV Infectionafter Oxymetholone Therapy: A Case Report

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Abstract: Aplastic anemia is a hematopoietic stem cell defect possibly due to an autoimmune process. It is characterized by the combination of the peripheral pancytopenia and hypocellular marrow. Besideshorse antithymocyte globulinwith cyclosporine orstem cell transplantation, oxymetholone, the synthetic androgen, is also allowed to be the alternative treatment for the patients who had non-severe aplastic anemiaor could not access the sophisticated therapies. And herein, therole as the treatment of aplastic anemia complicated bythe human immunodeficiency virus (HIV) infection of oxymetholonewill be reported. He was a 40-year old Thai man who presented with pancytopenia, Hb 4.7 g%, WBC 2,650/mm^3, platelet 5,000/mm^3, N 23 %, L 62 %, and diffuse medullary aplasia in the bone marrow, no evidence of HIV infection. He was treated with oxymetholone 150 mg a day and the regular blood transfusion every 1-3 months for keeping his Hb level 7 g% or more. Two years later, HIV antigen/antibody wasfound positive. The CD4 count was 437/mm^3 or 31 %, andanti-retroviral therapy was neverinitiated. Every year, hematologic parameters as well as CD4 count were gradually increased during long term oxymetholone therapy without the drug side effect or any opportunistic infection until transfusion was finally not necessary althoughthe viral load had never beenstudied through the long follow-up period. The present hematologic parameters were: Hb 13.0 g%, WBC 5,300/mm^3, platelet 24,000/mm^3, and CD4 526/mm^3. Both AA and the CD4 count in our case seemed to slowly respond to oxymetholone therapy without the anti-retroviral regimen.

Key words: Aplastic Anemia, HIV Infection, Oxymetholone

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บทคัดย่อ: โรคไขกระดูกฝ่อ และการติดเชื้อเอชไอวีดีขึ้นหลังจากได้รับการรักษาด้วยยาอ็อกซี่เมโธโลน: รายงานผู้ป่วย 1 ราย

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โรคไขกระดูกฝ่อ (aplastic anemia) เป็นโรคที่เกิดจากความผิดปกติของเซลล์ต้นกำเนิดของเม็ดเลือด ซึ่งอาจจะเนื่องมาจากกระบวนการทาง autoimmune ก็เป็นได้ ผู้ป่วยจะมีเม็ดเลือดขาว เม็ดเลือดแดง และเกล็ดเลือดต่ำในกระแสเลือดต่ำ (pancytopenia) ร่วมกับการมีเซลล์ในไขกระดูกต่ำด้วย การรักษานอกจากจะใช้ horse antithymocyte globulin with cyclosporine หรือ การปลูกถ่ายเซลล์ต้นกำเนิดแล้ว ยังอาจจะใช้ oxymetholone ซึ่งเป็นฮอร์โมนเพศชายสังเคราะห์สำหรับผู้ป่วยที่อาการของโรคไม่รุนแรง หรือผู้ป่วยที่ไม่สามารถเข้าถึงการรักษาที่วิจิตรบรรจงได้ ในการศึกษานี้จะแสดงถึงบทบาทของ oxymetholone ในการรักษาผู้ป่วยไขกระดูกฝ่อที่มีภาวะแทรกซ้อนด้วยการติดเชื้อเอชไอวี (human immunodeficiency virus หรือ HIV) ผู้ป่วยเป็นชายไทย อายุ 40 ปี ตรวจเลือดพบว่า Hb 4.7 กรัม%, WBC 2,650/มม^3, platelet 5,000/มม^3, N 23 %, L 62 %, ร่วมกับภาวะไขกระดูกกลายเป็น diffuse medullary aplasia ขณะนั้นยังไม่พบหลักฐานการติดเชื้อเอชไอวี ให้การรักษาด้วย oxymetholone 150 มก. ต่อวัน พร้อมกับการให้เลือดทุก 1-3 เดือน เพื่อรักษาระดับ Hb ให้เท่ากับ 7 กรัม% หรือ มากกว่า 2 ปีต่อมาตรวจเลือดซ้ำอีกพบว่ามี HIV antigen/antibody ให้ผลบวก, CD4 count 437/มม^3 หรือ 31 %, ยังไม่ได้เริ่มยากลุ่มต้านไวรัสเอชไอวี แต่ยังคงให้การรักษาด้วย oxymetholone ต่อไป นัดตรวจตลอดพบว่า ผลเลือด และค่า CD4 count ค่อย ๆ เพิ่มขึ้นในแต่ละปี โดยไม่มีผลข้างเคียงจากยา หรือการติดเชื้อฉวยโอกาสเลย จนไม่มีความจำเป็นต้องเพิ่มเลือดให้อีกต่อไป แต่ไม่มีการตรวจระดับปริมาณไวรัสเลยตลอดเวลาหลายปี ที่ติดตามการรักษาล่าสุดผลตรวจเลือดเป็น Hb 13.0 กรัม%, WBC 5,300/มม^3, platelet 24,000/มม^3, และ CD4 526/มม^3 ทั้งโรคไขกระดูกฝ่อและระดับ CD4 count ของผู้ป่วยรายนี้ดูเหมือนตอบสนองต่อการรักษาด้วย oxyme-tholone อย่างช้า ๆ โดยไม่ต้องให้การรักษาด้วยยากลุ่มต้านไวรัสเอชไอวีเลย

คำสำคัญ: ไขกระดูกฝ่อ, การติดเชื้อเอชไอวี, อ็อกซีเมโธโลน

Introduction

Aplastic anemia is an acquired hematopoietic stem cell defect leading to the decreased hematopoietic cell precursors in the bone marrow and the peripheral pancytopenia. Itsbasic pathogenesis is believed to be an immune mediated,viz., the autoreactive lymphocy-tes mediate the destruction of hematopoietic stem cells. Exposures to drugs, viruses, and toxins, are thought to trigger the aberrant immune response in some patients, but most cases are classified as idiopathic[1]. The important and effective treatment for severe aplastic anemia, reticulocyte <20,000/mm^3, neutrophil <500/mm^3, platelet <20,000/mm^3 and cellularity <25 % in bone marrow[2], includes the horse antithymocyte globulin with cyclosporin, and the stem cell tran-splantation in cases of available compatible donors[3].

Oxymetholone is a synthetic androgen which has been accepted by the US FDA to treat the patients with inadequate production of the red blood cells due to bone marrow failure such as aplastic anemia, congenital or acquired[4], and sickle cell anemia[5]. Other indications may include fatigue and wasting in HIV-infected persons[6]. The aim of this study was to report the role of oxymetholonein the treatment of the patient with aplastic anemia who was later complicatedbyan HIV infection.

Case Report

A 40-year-old Thai man was finallyfound to recover nearly completely from aplastic anemia and CD4 lymphocytopenia during HIV infection after oxymetholone therapywithout anti-retroviral regimen for many years, Hb 13.0 g% Hct 40.6 %, WBC 5,300/mm^3, platelet 24,000/mm^3.

In 2010, he was definitely diagnosed as having aplastic anemia based on the combination of the peri-pheral pancytopenia and the diffuse medullary aplasia in the bone marrow biopsy specimen, Hb 7.1 g%, WBC 2,700/mm^3, platelet 5,300/mm^3, N 23%, L 62 %, reticulocyte 0.8 %, MCV 97.9 fL, MCH 32.9 pg, erythropoietin >200 (2.6-34.0), normal liver and kidney function tests, albumin 4.2 g%, globulin 3.2 g% and negative for HIV antibody. And he was treated with oxymetholone 150 mg a day. He regularly atten-ded our clinic every 1-3 months and he would be tran-sfused if his Hbconcentration was less than 7.0 g%.

In 2012, he was tested again and found to have positive HIV antigen/antibody, negative for VDRL, HBsAg, anti-HCV and anti-HAV IgM, CD4 count 437/mm^3 or 31 %. The anti-retroviral therapywas not-initiated but the treatment with oxymetholone was continued.

His hematologic parameters including CD4 count were gradually improved every year as shown in table.

year	Hb (g%)	WBC (/mm^3)	Platelet (/mm^3)	CD4 (/mm^3)
2010	7.1	2,700	7,000	-
2011	6.6	2,200	4,000	-
2012	7.3	2,800	14,000	437
2013	9.1	3,800	14,000	439
2014	10.2	3,800	20,000	460
2015	13.0	5,300	24,000	526

No any opportunistic infection was recognized during the long term follow-up. Since 2013 he did notneed the blood transfusion.In 2015, the dose of oxymetholone was lowered to be 100 mg a day after his Hb concentration was up to 13.0 g% and he could maintain his Hblevel and the WBC count within the normal range although the platelet count was still profoundly low. The antiretroviral therapy was still withheld whereas the CD4 count was gradually increased every year.

For the side effects of oxymetholone, no gynecomastia was seen. The body weight, liver func-tion and kidney function tests were not changed.

Discussion

In HIV-infected persons, AA can be more commonly found than usual because the HIV can indirectly damage the hematopoietic stem cells, in the bone marrow leading to decreased production of one, two or all three cell lines resulting in AA[7,8]. On the other hand, the aplastic anemia patients always need frequent blood transfusion and this can contribute the risk of HIV infectioneven in cases of transfusion

with the HIV-negative blood[9,10]. Our case was firstly found negative but later positive for HIV antibody. Itwas nottraced back whether he got infection from transfusion.

In the study of 31 patients with idiopathic or drug-induced AA, oxymetholone, 3-5 mg/kg/day for 2 months and then 1.5-2 mg/kg/day, was found clinically and hematologically effective, 10 with partial remission and 1 with complete remission[11]. Oxymetholone was firstly found to slightly increase Hb levelin our case at the end of the second year of treatment and further gradually improve the Hb concentration although he was complicated by HIV infection.

During the long term oxymetholone therapy, the CD4 count had been gradually increased until it was more than 500/mm3 although the HAART therapy had never been initiated. So far the effect of oxy-metholoneupon the CD4 count is inconclusive, 50 mg a day of oxymetholonein conjunction with testosterone replacement in HIV-infected men does not affect the CD4 level[12]. But oxymetholone 50 mg a day in combi-nation with proteinase inhibitors can increase CD4 value overtime[13]. While in double-blind, randomized, placebo-controlled trial of oxymetholone for HIV-related wasting syndrome, the increase of CD4 is found in the oxymetholone 100 mg a day group but not found in the 150 mg a day of oxymetholone group or placebo group and the investigators conclude that the increment is the effect of the intensification of HAART instead[14]. However, the effect of oxymetho-lone 100-150 mg a day for augmentation of the CD4 in HIV-infected patients should be further verified.

Oxymetholone is demonstrated to increase the body weight as compared with the placebo in cases with eugonadal males and females with HIV infection[14] but the increased body weight as well as other side effects was not seen in our case.

Conclusion

A 40-year old Thai man was definitely diagnosed as aplastic anemia complicated by HIV infection. He wascontinuously treated withoxyme-tholone 150 mg a day without HAART. Within 5 years, the Hb, WBC and platelet were gradually improved every year from 7.1 g%, 2,700/mm^3 and 7,000/mm^3 to be 13.0 g%, 5,300/mm^3 and 24,000/mm^3, respec-tively while the CD4 count was augmented from 437 to be 526/mm^3. The role of oxymetholone for increasing the CD4 count in HIV-infected patients should be systemically further verified.

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