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S Insiripong

W Yingsitsiri

J Boondumrongsagul

J. Noi wattanakul

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## Aplastic anemia in HIV-infected persons

Somchai Insiripong\* Watcharin Yingsitsiri\*

Juree Boondumrongsagul\* Jirawadee Noi Wattanakul\*

**Insiripong S, Yingsitsiri W, Boondumrongsagul J, Noi Wattanakul J. Aplastic anemia in HIV-infected persons. Chula Med J 2014 May – Jun; 58(3): 247 - 54**

- Background** : *Aplastic anemia (AA) is fatal. Its common causes are drugs, chemicals and viruses as well as HIV. However, AA in HIV-infected persons has been rarely reported.*
- Objective** : *To study AA in HIV-infected persons.*
- Design** : *Retrospective descriptive study.*
- Setting** : *Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima.*
- Participants and Methods** : *All patients with pancytopenia and proved to have HIV infection and bone marrow cellularity <25% in 2012 - 2013, were recruited. Patients with other secondary causes of AA were excluded.*
- Results** : *From 270 cases with AA, eleven cases (4.1 %) had HIV infection. All had cellularity <25 % in the bone marrow. Five of them were taking ARV before AA was diagnosed. The CD4 had positive correlation with absolute lymphocyte count but negative correlation with platelet count. They were all treated with oxymetholone and ten with low CD4 count were treated with ARV therapy.*

\*Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

**Conclusion** : *There were eleven from 270 cases with AA having HIV infection during the two-year period. It is proposed that the HIV itself rather than ARV therapy is related to AA.*

**Keywords** : *Aplastic anemia, HIV-infected patients.*

Reprint request: Insiripong S. Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000.

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- เหตุผลของการวิจัย** : ไขกระดูกฝ่อ เป็นโรคร้ายแรง สาเหตุที่พบบ่อยได้แก่ ยา สารเคมี และการติดเชื้อไวรัส ซึ่งรวมถึงเชื้อเอดส์ด้วย แต่รายงานโรคไขกระดูกฝ่อจากเชื้อไวรัสเอดส์ยังมีน้อย
- วัตถุประสงค์** : ศึกษาผู้ป่วยไขกระดูกฝ่อในผู้ติดเชื้อไวรัสเอดส์
- รูปแบบการวิจัย** : การศึกษาย้อนหลังเชิงพรรณนา
- สถานที่ทำการศึกษา** : กลุ่มงานอายุรกรรม รพ.มหาราชนครราชสีมา จ.นครราชสีมา
- ตัวอย่างและวิธีการศึกษา** : ผู้ที่มี pancytopenia ในปี 2555 - 2556 ตรวจไขกระดูกพบว่า เป็นไขกระดูกฝ่อ และตรวจเลือดพบติดเชื้อเอดส์
- ผลการศึกษา** : มีผู้ป่วยไขกระดูกฝ่อ 270 ราย ติดเชื้อเอดส์ 11 ราย (ร้อยละ 4.1) ทุกรายมีเซลล์ในไขกระดูกน้อยกว่าร้อยละ 25 มี 5 ราย รับประทาน ARV อยู่ก่อนแล้ว พบว่าระดับ CD4 มีความสัมพันธ์เชิงบวกกับจำนวน absolute lymphocyte และความสัมพันธ์เชิงลบกับระดับเกล็ดเลือด ทุกรายได้รับการรักษาด้วย oxymetholone ส่วนผู้ป่วย 10 ราย ที่มี CD4 ต่ำจะได้รับยา ARV ด้วย
- สรุป** : ผู้ป่วยไขกระดูกฝ่อ 270 ราย มีผู้ติดเชื้อเอดส์ 11 ราย ในเวลา 2 ปี เชื่อว่าไขกระดูกฝ่อเกี่ยวข้องกับเชื้อไวรัสเอดส์มากกว่ายาต้านไวรัส
- คำสำคัญ** : โรคไขกระดูกฝ่อ, ผู้ติดเชื้อเอดส์.

Aplastic anemia (AA) is characterized by the decrease of the hematopoietic stem cells in the bone marrow leading to pancytopenia in the peripheral blood.<sup>(1)</sup> The clinical manifestations are normocytic normochromic anemia, purpura of the skin or mucosa or bacterial infection without hepatosplenomegaly. The causes which can be identified in minority of cases comprise drugs, chemicals, radiation, infection from any of the following organisms such as hepatitis B virus, CMV and HIV.

HIV may affect blood cells, leading to various kinds of cytopenias from the decreased production or the peripheral destruction. Anemia, the most common cytopenia, is found in 24.2 - 95%<sup>(2)</sup>, leucopenia in 26.8% and thrombocytopenia in 16.1%. The higher prevalence of any cytopenia is directly related to the degree of immunosuppression.<sup>(3)</sup> Not only HIV itself but also the various drugs for the treatment of HIV or its complications, causes cytopenia. However, in most cases of HIV cytopenia, the bone marrow biopsy almost always shows normocellular or hypercellular marrow reflecting myeloid dysplasia and ineffective hematopoiesis.<sup>(4)</sup>

Among HIV patients with pancytopenia, 50% show granulomas (2/3 positive for AFB, 1/3 positive for cryptococci); 25% show hemophagocytosis; and the last 1/4 have no specific pathology.<sup>(5)</sup> AA has rarely been found in HIV-infected persons<sup>(6)</sup>, for instance, only one from 50 ARV naive HIV-infected patients with anemia is shown to have aplastic anemia.<sup>(7)</sup> This study was aimed to review the cases of AA found in HIV-infected persons.

## Participants and Methods

This retrospective study recruited the patients

who were referred to the Department of Medicine, Maharat Nakhon Ratchasima Hospital, with the problems of the gradual onset of moderate to severe anemia with thrombocytopenia and leucopenia. In 2012 and 2013, there were 132 and 138 cases (total 270 cases) of aplastic anemia, respectively, attending hematology clinic, department of medicine. All were diagnosed as AA, depending on the combination of reticulocyte  $<20,000/\text{mm}^3$ , the cellularity  $<25\%$  in the bone marrow biopsy, with neutropenia or thrombocytopenia. Of these, eleven patients were found to have positive HIV antibody (4.1 %) and only five of them fulfilled the criteria of severe AA (bone marrow cellularity  $<25\%$ , reticulocyte  $<20,000/\text{mm}^3$  with either neutrophil  $<500/\text{mm}^3$  or platelet  $<20,000/\text{mm}^3$ ).<sup>(8)</sup>

The patients who had HIV infection with pancytopenia due to histoplasmosis, tuberculosis or granuloma in the bone marrow were excluded from our study.

The CD4 count and other infectious agents including hepatitis virus B and C, VDRL and other blood tests consisting of the liver function, kidney function tests and antinuclear antibody were also evaluated.

## Results

There were eleven patients recruited, six males and five females. Their ages ranged from 35 to 42, mean  $39.0 \pm 2.6$  years. The diagnosis of AA was established while five from eleven patients (45.4%) had been taking the antiretroviral (ARV) drugs which consisted nevirapine, lamivudine and stavudine and two of these also concurrently took co-trimoxazole and fluconazole. The duration of ARV therapy ranged from

4 months to 40 months, mean  $17.4 \pm 14.7$  months.

Of the eleven cases, there were one with HBV and one with HCV but no one had positive VDRL.

The CBC and the CD4 count of all eleven patients are shown as follows.

They were all treated with oxymetholone (Androlic®) 150 mg a day without anti-thymocyte globulin or stem cell transplantation. Ten from the eleven cases that had CD4 count  $< 350/\text{mm}^3$  were also treated with the ARV drugs as well as other

Sex	Age	Hb	WBC	Platelet	N	L	CD4
M	39	5.6	1,500	117,000	1,309	91	3
F	42	8.4	2,800	93,000	1,400	896	135
M	41	8.6	900	39,000	450	342	188
F	39	7.8	700	10,000	207	437	219
F	35	8.9	2,600	96,000	1,058	702	19
M	36	2.6	1,300	29,000	429	767	171
F	38	7.4	1,000	75,000	480	520	18
M	39	8.3	2,400	110,000	1,632	432	5
M	42	5.5	2,300	12,000	414	1,280	432
F	42	10.5	2,300	65,000	2,070	207	45
M	36	10.4	2800	37,000	1,848	504	74

There were only five patients had neutrophil  $< 500/\text{mm}^3$  whereas only two had platelet count  $< 20,000/\text{mm}^3$ .

The mean  $\pm$  SD of the Hb concentration, WBC, platelet, absolute neutrophil count (ANC) and absolute lymphocyte count were found to be  $7.6 \pm 2.3$  g%,  $1,872.7 \pm 802.6/\text{mm}^3$ ,  $62,090.9 \pm 38,821.3/\text{mm}^3$ ,  $1,027.0 \pm 662.2/\text{mm}^3$  and  $561.6 \pm 335.0/\text{mm}^3$ , respectively.

The CD4 count ranged from 3 to 432, mean  $119.0 \pm 130.3/\text{mm}^3$ . There was only one patient with CD4 count  $> 350/\text{mm}^3$ .

The Pearson's correlation co-efficient (r) between the CD4 count and the Hb level, WBC, platelet, ANC and the lymphocyte count were calculated to be -0.369, -0.134, -0.777, -0.582 and 0.691, with p-value 0.264, 0.694, 0.005, 0.060, and 0.019, respectively.

supportive treatments such as the packed red blood cell transfusion to keep the Hb concentration to be  $> 7 - 8$  g%, empirical antibiotics for any episode of febrile neutropenia or platelet concentrate transfusion in cases of serious bleeding symptom.

## Discussion

The presumed pathogenesis of AA is the autoimmune process<sup>(9,10)</sup> as 70% of AA patients improve with the immune suppressive therapy. Hirano *et al.* show that 7 of 18 AA patients have an immunoglobulin G antibody to one of the genes, kinectin which is expressed in all hematopoietic cell lineages tested including CD34 + cells and no response to kinectin in healthy volunteers, multiply transfused non-AA patients, or patients with other autoimmune diseases.<sup>(9)</sup> AA is an organ-specific

T-cell-mediated disease localized in the bone marrow and several proteins in serum are proposed to be its autoantigen<sup>(11)</sup> while the HIV infection may alter the immune response leading to the formation of autoantibodies especially anticardiolipin and denatured DNA antibody.<sup>(12)</sup> However, the antimoesein antibody, that is generally found in 37% AA cases<sup>(13)</sup>, is not mentioned in the study of the autoantibody in HIV-infected persons.

The effects of HIV on the hematopoietic stem cells (HSC) appear to be indirect, as HSC are highly resistant to HIV infection despite the presence of surface receptors for HIV, except HIV-1 subtype C that is demonstrated to infect the HSCs *in vitro*.<sup>(14)</sup> Stem transduction can be achieved with HIV constructs in which the envelope glycoproteins have been replaced by vesicular stomatitis virus G protein. Therefore, HSC are likely participants in HIV-related cytopenias, but they are spared direct infection and can serve as a resource for cellular therapies for AIDS.<sup>(15)</sup>

Zidovudine is the most common cause of ARV-related anemia<sup>(16)</sup> but the ARV regimen, taken by our five patients (45.4 %) who develop AA during ARV therapy, does not contain zidovudine. Although lamivudine can also cause anemia<sup>(17)</sup>, almost all cases of anemia related to ARV regimen are solely diagnosed as the pure red cell aplasia, not AA.

The CD4 count has no correlation with the Hb level<sup>(7)</sup>, WBC and ANC but it has positive correlation with absolute lymphocyte count and negative correlation with the platelet count with statistic significance. The direct correlation between the absolute lymphocyte count and the CD4 count

has been demonstrated for many years.<sup>(18)</sup> Sloan *et al.* showed that the incidence of thrombocytopenia ( $<150,000/\text{mm}^3$ ) in HIV-infected patients increases with progressive immune suppression<sup>(19)</sup> but the degree of thrombocytopenia is not related to the progress to AIDS.<sup>(20)</sup> The negative correlation between the platelet count and the degree of immunosuppression in our study does not conform with the result of other study<sup>(3)</sup>, probably because, the mechanisms of low platelet count in our HIV-infected patients are multifactorial, either increased destruction or decreased production, from HIV itself, drugs or malnutrition.

There is no definite guideline for effective treatments for AA in HIV-infected patients, it may be the ARV therapy alone<sup>(6)</sup>, stem cell transplantation<sup>(21)</sup>, or androgen treatment that is particularly proved effective in the AA with a heterozygous hTERT gene mutation although this gene has not been explored in our series.

## Conclusion

Eleven cases of AA in HIV-infected persons are studied. All have pancytopenia and hypocellularity of the hematopoietic cells in the bone marrow biopsy ( $<25\%$  cellularity). Five are diagnosed as AA during the ARV therapy. The CD4 count does not correlate with the Hb level, WBC and ANC but has positive correlation with absolute lymphocyte count and negative correlation with platelet count. They are all treated with oxymetholone and ten are also treated with ARV because CD4 count is  $< 350/\text{mm}^3$ . It is proposed that the HIV itself rather than ARV is related to AA.

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