Thrombocytopenia in HIV-infected patients, Islamic Republic of Iran

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نقص صفيحات الدم في المصابين بعدوى فيروس الإيدز في كرمانشاه في جمهورية إيران الإسلامية

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الخلاصة: إن نقص صفيحات الدم يمثّل أحد اعتلالات الدم المرتبطة بالإيدز والتي قد تنتج من ازدياد الحِمْل الفيروسي وتضاؤل عدد اللمفاويات CD4. وقد قمنا بتقييم معدل نقص صفيحات الدم (نقص الصفيحات عن مئة ألف صفيحة دموية في كل مكرولتر) في 170 من المرضى المصابين بعدوى فيروس الإيدز (161 من الذكور و9 من الإناث) بدءاً من شهر أيار/مايو 2000 وحتى شهر نيسان/أبريل 2001 في كرمانشاه في جمهورية إيران الإسلامية. وقد كانت النسوة المدروسات جميعهن باستثناء سبع منهن يتعاطين المخدرات بطريق الحقن فيما كان لدى 34 منهن نقص صفيحات الدم، ومنهن 3 يعانين من نقص شديد في صفيحات الدم (تقل صفيحات الدم عندهن عن 20 ألف صفيحة دموية في كل مكرولتر). ورغم أن معدلات انتشار نقص صفيحات الدم متشابهة في مختلف مراحل العدوى بفيروس العوز المناعي البشري (18.5٪ – 22.5٪) فإن النقص الوخيم لصفيحات الدم لوحظ لدى المرضى الذين تقل لديهم أعداد الخلايا التائية CD4 عن مئتي خلية في كل مكرولتر. و لم يكن هناك حالات مرافقة أخرى، وكان النقص المتوسط الشدة في صفيحات الدم شائعاً بين المرضى المصابين بفيروس العوز المناعي البشري في إقليمنا، وكان معدل النقص في الصفيحات ثابتاً طوال مراحل العدوى بفيروس الإيدز، إلا أن الأنماط الوخيمة شائعة في الحالات المتفاقمة.

ABSTRACT Thrombocytopenia is a blood dyscrasia common in AIDS patients that may result from increased viral load and diminished CD4 T lymphocytes. We evaluated the rate of thrombocytopenia (platelet count < 100 000/μL) in 170 HIV-infected patients (161 males and 9 females) from May 2000–April 2001 in Kermanshah, Islamic Republic of Iran. All except 7 females were injecting drug users. While 34 patients had thrombocytopenia, 3 had severe thrombocytopenia (platelet count < 20 000/μL). Although prevalence was similar in various stages of HIV infection (18.5%–22.5%), severe thrombocytopenia was in patients with CD4 T cell count < 200 cells/μL. There were no other associated conditions. Mild thrombocytopenia is common in HIV-infected patients in our region.

La thrombopénie chez des patients infectés par le VIH à Kermanshah (République islamique d'Iran)
RESUME La thrombopénie est une dyscrasie associée au SIDA qui peut résulter d'une augmentation de la charge virale et d'une diminution des lymphocytes T-CD4. Nous avons évalué le taux de thrombopénie (numération plaquettaire < 100 000/μL) chez 170 patients infectés par le VIH (161 hommes et 9 femmes) de mai 2000 à avril 2001 à Kermanshah (République islamique d'Iran). Tous les patients sauf 7 femmes étaient des consommateurs de drogue par injection. Si 34 patients avaient une thrombopénie, 3 avaient une thrombopénie sévère (numération plaquettaire < 20 000/μL). Même si la prévalence était similaire aux différents stades de l'infection à VIH (18,5 %–22,5 %), on trouvait une thrombopénie sévère chez les patients ayant une numération de lymphocytes T-CD4 inférieure à 200 cellules/μL. Il n'y avait pas d'autre pathologie associée. Une thrombopénie bénigne est courante chez les patients infectés par le VIH dans notre région.

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Introduction

A common AIDS-related blood dyscrasia is thrombocytopenia, which is the result of mechanisms such as cell destruction by the immune system, ineffective haematopoiesis and drug side-effects [*1*]. In some patients, thrombocytopenia is an isolated haematologic abnormality with elevated levels of platelet surface-binding immunoglobulins and normal or increased megakaryosis. These patients are designated as having thrombocytopenic purpura [*2,3*]. Thrombocytopenia is defined as platelet count < 100 000 per microlitre of blood; severe thrombocytopenia is platelet count < 20 000 per microlitre of blood.

Thrombocytopenia is associated with all types of HIV infection acquired by all routes of transmission but it has been reported with increased prevalence among injecting drug users (IDUs) and among people of older age and white race [*4*]. In one study, 90% of 321 HIV-positive IDUs had platelet counts of less than 100 000/μL compared with 3% among 395 homosexual HIV-infected individuals [*5*]. Among 1004 HIV-infected patients, thrombocytopenia occurred in 21% of patients with full-blown AIDS and 30% of patients with CD4 T lymphocytes < 200 cells/μL without clinical AIDS. In patients with CD4 T lymphocyte counts between 200 and 500 cells/μL, the rate of thrombocytopenia was 4% in symptomatic patients in comparison with 8% among asymptomatic patients [*6*].

It has been postulated that immune complex deposition in platelet membranes with consequent clearance by the reticuloendothelial system is the main cause of thrombocytopenia in HIV-infected patients [*7,8*]. HIV-associated thrombocytopenia may be the initial manifestation of HIV infection before the appearance of other AIDS-defining indicators [*2*]. In one report, thrombocytopenia was observed commonly in cases with CD4 T lymphocyte counts between 300 and 600 cells/μL [*9*]. This was in accordance with a study that demonstrated the occurrence of thrombocytopenia in intermediate phases of the infection [*10*].

Most studies have evaluated the use of zidovudine and have shown increased platelet production [*11*]. Combination therapy also resulted in sustained platelet increases [*12*]. When antiretroviral agents fail to improve the platelet count or cannot be used, other therapies similar to those used in 'classic' immune thrombocytopenia can be employed, including corticosteroids, intravenous infusions of immune globulin or splenectomy. Of note, follow-up of heavily treated patients showed no acceleration of CD4 decline and no change in plasma viral load measurements.

Splenectomy has been used to treat HIV-positive patients with refractory thrombocytopenia. Although it is an effective therapy, there are concerns about infections and the selection of appropriate candidates. The latest evidence indicates that the chemokine receptor CXCR4 (co-receptor for the cellular entry of lymphotropic HIV strains) is expressed on megakaryocytes; as a result, the development of chemokine receptor antagonists may modify the course of the disease [*11,12*].

Thrombocytopenia is thought to be a marker of progression to advanced phases in HIV infection and most patients have mild to moderate thrombocytopenia with no clinical symptoms [*2,9*].

In this study, we evaluated HIV-infected patients (most of whom acquired the infection through intravenous drug use) for thrombocytopenia according to epidemiological, clinical and immunological fea-

tures. We aimed to determine the prevalence of thrombocytopenia among this group.

Methods

From May 2000 to April 2001, 170 HIV-infected patients referred voluntarily to the HIV/AIDS Counselling and Care Centre in Kermanshah City, Kermanshah Province, Islamic Republic of Iran, were evaluated for platelet count by Coulter counter. All patients were informed about the study and samples were coded. Due to the lack of funds, no patient in the study was receiving antiretroviral therapy. The cases were divided into 3 groups according to thrombocyte count: less than 20 000/μL blood, between 20 000 and 100 000/μL and more than 100 000/μL blood.

Thrombocytopenia was defined as a platelet count of less than 100 000/μL blood. Each patient with thrombocytopenia underwent precise medical history, clinical examination and flow cytometric analysis for different T cell markers. Abdominal sonography was performed for all patients with severe thrombocytopenia (platelet counts < 20 000/μL blood). There were no associated infections, pancytopenia, drug consumption, kidney dysfunction, splenomegaly or other conditions to cause thrombocytopenia in the patients except for HIV infection.

The rate of thrombocytopenia and its correlation with sex, age and CD4 T cell count were statistically analysed by ANOVA and Student *t*-test. *P*-value < 0.05 was significant. Liver and kidney function tests of all cases were normal. (Patients with severe kidney dysfunction were excluded from the analysis.)

Results

Based on the blood analysis, the white blood cell and reticulocyte counts of all cases were normal and only 17 patients (10%) had mild isolated anaemia (haemoglobin level between 10 g/dL and 12 g/dL). No thrombocytopenia occurred in the form of pancytopenia. Of the 170 patients, 161 (94.7%) were male and 9 (5.3%) were female. All males (100%) and 2 females (12%) were IDUs. Table 1 shows that only men had thrombocytopenia; 34 men (20%) had platelet counts < 100 000/μL and among them 3 (1.8%) had severe thrombocytopenia (platelet counts < 20 000/μL blood). The mean count for mild thrombocytopenia cases was 66 000/μL and for severe cases, 11 300/μL blood.

No patients younger than age 20 years had thrombocytopenia. Of 114 HIV-infect-

Table 1 **Prevalence by sex of thrombocytopenia among HIV-positive patients**

Sex	Platelets ≥ 100 000/μL blood		Platelets 20 000 to < 100 000/μL blood		Platelets < 20 000/μL blood		Total	
	No.	%	No.	%	No.	%	No.	%
Men	127	78.9	31	19.2	3	1.9	161	100
Women	9	100	0	0	0	0	9	100
Total	136	80.0	31	18.2	3	1.8	170	100

ed patients in the 20–40-year-old age group, 24 patients (21%) were thrombocytopenic. Of 53 patients in the 40-year-old and older age group, 10 patients (19%) were thrombocytopenic. The difference in thrombocytopenia between the 2 age groups was not significant (Table 2).

The rate of thrombocytopenia was slightly higher among patients with CD4 T lymphocyte counts less than 200 cells/μL (22.5%) than among those with CD4 T lymphocyte counts between 200 and 500 cells/μL (18.5%) or more than 500 cells/μL (18.5%) but the difference was not statistically significant (Table 3). However, the mean CD4 T cell count was significantly lower in patients with severe thrombocytopenia ($P < 0.05$) (Table 4).

Among the patients with severe thrombocytopenia, only 1 case developed spontaneous skin ecchymosis. Abdominal sonography did not find splenomegaly in any severely thrombocytopenic patients. Only 1 patient with severe thrombocytopenia (platelet count = 8000/μL) underwent splenectomy due to persistent haemorrhaging and thrombocytopenia despite steroid therapy with resultant dramatic and persistent increase in platelet count (250 000/μL) and resolution of clinical signs.

Table 2 **Prevalence of thrombocytopenia among HIV-infected patients according to age group**

Age group	Platelets > 100 000/μL blood		Platelets 20 000 to < 100 000/μL blood		Platelets < 20 000/μL blood		Total	
	No.	%	No.	%	No.	%	No.	%
<20	3	100	0	0	0	0	3	100
20–40	90	79	21	19	3	2	114	100
>40	43	81	10	19	0	0	53	100
Total	136	80	31	18.2	3	1.8	170	100

Table 3 **Prevlence of thrombocytopenia among HIV-infected patients according to CD4T cell count**

CD4T cell count (cells/μL)	Platelets > 100 000/μL blood		Platelets < 100 000/μL blood		Total	
	No.	%	No.	%	No.	%
<200	48	77.5	14	22.5	62	100
200–500	66	81.5	15	18.5	81	100
>500	22	81.5	5	18.5	27	100
Total	136	80.0	34	20	170	100

Table 4 **Mean CD4 T cell lymphocyte count according to severity of thrombocytopenia**

CD4 count (cells/μL)	Mild thrombocytopenia Platelets 20 000 to < 100 000/μL blood	Severe thrombocytopenia Platelets < 20 000/μL blood
Mean	266	115

Discussion

The rate of thrombocytopenia in HIV-infected patients in our study was 20%. This exceeded the rate reported in a retrospective study in San Francisco (> 11%) and from the Multicenter AIDS Cohort Study of 1500 patients in pre-AIDS phase (6.7%) [*9,10*]. In another study of 516 HIV-infected patients, the prevalence of thrombocytopenia was 15.5% [*13*].

In our study, 95.8% of patients were IDUs; 20.8% of the IDUs in our study had thrombocytopenia. This contrasts with the results of another study in which 9% of 321 IDUs infected with HIV had thrombocytopenia [*5*].

There were no cases of thrombocytopenia among the females in our study, although only 2 women were IDUs and 3 had CD4 T cells of less than 200 cells/μL. Due to the small number of female patients in our study, this is not significant.

There was no significant difference in thrombocytopenia among the different age groups of our study. Of the thrombocytopenic patients, 70% were between the ages of 20 and 40 years. Since 114 (67%) HIV cases were between 20 and 40 years, the age distribution in patients with thrombocytopenia is similar to the general pattern of age distribution and it has no particular effect on age groups. In other studies, the rate of thrombocytopenia has been reported to be more common among older age groups [*4*].

One important finding of our study was that for patients with advanced immune suppression severe thrombocytopenia was more frequent. The mean of CD4 T cells for the severe cases was significantly lower than for the mild cases. All severe cases had CD4 T cell counts less than 200 cells/μL.

In contrast to the role of immunosuppression in severity of thrombocytopenia, there was no relation between prevalence of thrombocytopenia and stage of immunologic status based on CD4 T cell count. As Table 4 shows, the rate of thrombocytopenia in patients with CD4 T cell counts higher than 500 cells/μL was 18.5% in comparison with 18.5% and 22.5% among patients with CD4 T cell counts between 200 and 500 cells/μL and patients with CD4 T cell counts < 200 cells/μL respectively. Other studies have demonstrated increased prevalence of thrombocytopenia in advanced or intermediate stages of HIV infection [*3,9,10*]. Thus, we believe that despite advanced severity of thrombocytopenia with advancing HIV infection, there was no increase in the overall rate of thrombocytopenia with stage of infection [*2*].

We did not identify any underlying factors contributing to thrombocytopenia in the patients including drug consumption, splenomegaly and associated infections. Due to the lack of anti-HIV drugs in our province during this time, none of the patients (even those with CD4 T cell lympho-

cytopenia) received any antiretroviral medications that could have affected the thrombocytopenia. Therefore, we suggest that HIV infection per se is the main cause of thrombocytopenia in our patients. HIV infection as the main cause of thrombocytopenia seems to be more common here than in other regions of the world.

We propose further studies to evaluate the rate of thrombocytopenia in other groups at risk for HIV as almost all cases in our study were IDUs. Measuring antiplatelet antibodies and thrombopoietin levels of HIV patients with and without thrombocytopenia could also lead to a better understanding of the pathogenesis of this dyscrasia. Evaluation of combination therapy efficacy in the treatment of severe thrombocytopenia is also needed [*14,15*].

Although we had dramatic results from the splenectomy for one of our patients, more cases must be evaluated to validate the role of this procedure in treatment. Already some studies have demonstrated its beneficial effects with 80%–100% response rates [*15–19*].

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