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Prevalence and associated factors of thrombocytopenia among human immunodeficiency virus-infected patients at a tertiary care hospital in İzmir, Turkey

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Background/aim: The aim of this study was to determine the prevalence and associated factors of thrombocytopenia in human immunodeficiency virus (HIV)-infected patients.

Materials and methods: A cross-sectional study was conducted in a tertiary care hospital in İzmir, Turkey. All HIV-infected patients admitted to the Department of Infectious Diseases and Clinical Microbiology between 2006 and 2011 were recruited. Patients with thrombocytopenia at any time point were defined as the case group and the remaining patients were defined as the control group.

Results: The frequency of thrombocytopenia was 35.8%. Thrombocytopenia was more frequent in patients with acquired immune deficiency syndrome (AIDS) than in patients without AIDS ($P < 0.05$) and in antiretroviral-naive patients than in patients on combination antiretroviral therapy (cART) or those who had ever used cART in the past ($P < 0.05$). Additionally, rates of tuberculosis infection, prophylactic use of trimethoprim-sulfamethoxazole (TMP/SMX), and being anti-HCV seropositive at any time point were higher in patients with thrombocytopenia than in the control group ($P < 0.05$), and the case group had lower CD4+ T lymphocytes at first admission ($P < 0.05$).

Conclusion: The main finding was the clear association between thrombocytopenia and advanced and uncontrolled HIV infection. Tuberculosis and HCV coinfections were also identified as associated factors for thrombocytopenia.

Key words: Thrombocytopenia, HIV, AIDS

1. Introduction

Hematologic abnormalities are one of the most frequent complications of human immunodeficiency virus (HIV) infection and a frequent cause of death in HIV-infected patients (1–6). HIV infection of lymphocytes, monocytes, and macrophages is thought to induce abnormalities in cytokine production that in turn affect hematopoiesis. In addition, infections, malignancies, and drug-induced myelosuppression contribute to the development of cytopenias in HIV-infected patients (2,7–9). Despite the frequency of cytopenias tending to increase as the disease progresses, thrombocytopenia (<150,000/μL) may occur in all stages of HIV infection (10–17). Cytopenias play an important role in HIV-related morbidity and have a major impact on quality of life (2,7–9). Before the introduction of combination antiretroviral therapy (cART), the prevalence of thrombocytopenia associated with HIV infection ranged from 5% to 30% (3,10,18–23). Thrombocytopenia was also identified as a poor prognostic factor for progression of HIV infection to acquired immune deficiency syndrome (AIDS) and death (3,4). Prolonged survival of HIV-infected patients after the introduction of cART may also cause new complications. Combination antiretroviral therapy may itself lead to hematological toxicities (24). Severe thrombocytopenia, which requires treatment and bleeding diathesis, can be seen in HIV-infected patients on cART (25).

A recently published study reported that the frequency of thrombocytopenia varied among countries and that the geographical distribution of thrombocytopenia differed from that of neutropenia and anemia in HIV-infected patients (26). Studies regarding the frequency of thrombocytopenia in HIV-infected patients in Turkey are very limited (27). The primary aim of this study was to determine the frequency of thrombocytopenia in HIV-infected patients followed in our clinic and the second

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purpose was to determine the factors associated with thrombocytopenia.

2. Materials and methods

This cross-sectional study was conducted in the Department of Infectious Diseases and Clinical Microbiology of a tertiary care hospital. All HIV-infected patients admitting to the department between January 2006 and December 2011 were consecutively recruited for the study. In this population, the frequency of thrombocytopenia was investigated. Patients with thrombocytopenia at any time point were defined as the case group and the remaining patients were defined as the control group. Consequently, the case and the control groups were compared regarding demographic (sex, age at the time of diagnosis), clinical (duration of HIV infection, duration of follow-up, clinical stage, treatment history, and comorbid diseases, malignancies, and opportunistic infections at any time point), and laboratory (plasma HIV-1 RNA, CD4+ T lymphocyte count, complete blood count) features. For the case group, duration and probable cause of thrombocytopenia; presence of anemia, leukopenia, and/or neutropenia; presence or history of bleeding; and the interventions for the treatment of thrombocytopenia were evaluated.

HIV infection was diagnosed in the presence of a reactive screening test (ELISA) result confirmed by a western blot analysis. Patients were staged according to CDC recommendations (28). Platelet count of <150,000/μL was considered as thrombocytopenia. Hemoglobin levels of <13.0 g/dL in males, <12.0 g/dL in females, and <11.0 g/dL in pregnant women were considered as anemia. Leukocyte counts of <4000/μL and neutrophil counts of <1500/μL were considered as leukopenia and neutropenia, respectively. Duration of HIV infection was defined as the time since first HIV diagnosis and the duration of follow-up was defined as the time between the first and the last admissions. Acute and chronic thrombocytopenia were defined as thrombocytopenia persisting <3 months and ≥3 months, respectively. Data were obtained by retrospective scanning of patient files and computer records between 1 May and 30 June 2012.

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., USA). Descriptive statistics (median, minimum and maximum values, mean, standard deviation, count, and percentage) were used to summarize the results. Differences in normally distributed continuous variables were analyzed using an independent samples t-test. Comparisons of skewed data were analyzed using the Mann–Whitney U test. The chi-square or Fisher's exact test was used to compare categorical variables between the 2 groups. $P < 0.05$ was considered as statistically significant and the null hypothesis was rejected.

3. Results

A total of 95 HIV-infected patients were evaluated. Total duration of follow-up was 403 patient-years. At first admission, the median CD4+ T lymphocyte count was 280 (range: 0–1380) cells/μL and the median plasma HIV-RNA level was 41,250 (range: <20–5,730,000) copies/μL:. Patient characteristics are shown in Table 1. Six (6.3%) deaths were found. Causes of death were AIDS in 2 patients and non-Hodgkin lymphoma, lung cancer, rectal squamous cell carcinoma, and liver cirrhosis in 1 patient each. Thrombocytopenia was found in 5 of the 6 patients who died.

Overall, thrombocytopenia was found in 35.8% (n = 34) of the patients. Prevalence decreased to 24.2% and to 10.5% if platelet count of less than 100,000/μL (23) and less than 50,000/μL (10) was used to define thrombocytopenia, respectively. The characteristics of these patients are presented in Table 2. Possible causes of thrombocytopenia were HIV/AIDS in 22 patients (64.7%), liver cirrhosis in 3 (8.8%) patients, and didanosine usage, acute hepatitis C and chemotherapy in 1 (2.9%) patient each.

Frequency of thrombocytopenia was similar in male (39.5%) and female (21.1%) patients ($P > 0.05$). There was no significant difference between the case and the control group regarding median age (37 and 38 years, respectively). When compared, thrombocytopenia was more frequent in patients in AIDS stages than patients not in AIDS stages of HIV infection ($P < 0.05$) and in cART-naive patients than in patients on cART or who had ever used cART in the past ($P < 0.05$). Additionally, rates of tuberculosis, prophylactic use of trimethoprim-sulfamethoxazole (TMP/SMX), and being anti-HCV seropositive at any time point were higher in the case group than the control group ($P < 0.05$). The case group also had a lower CD4+ T lymphocyte count at first admission ($P < 0.05$). No statistically significant differences were detected between the 2 groups regarding other characteristics. Comparisons of the 2 groups are shown in Tables 3 and 4. In addition to its association with thrombocytopenia, patients with tuberculosis also had a significantly lower CD4+ T lymphocyte count (median: 73.0, range: 1–686 cells/μL) than patients who did not have tuberculosis (median: 324, range: 0–1380 cells/μL) ($P < 0.05$).

4. Discussion

This study showed that thrombocytopenia was an important issue to consider in our cohort of patients. First, the prevalence was high. Secondly, thrombocytopenia was accompanied by pancytopenia in almost half (44%) and complicated by bleeding in more than 1/10 (12%) of the patients. Lastly, although the rate of patients with AIDS diagnosis was different in patients with and without thrombocytopenia (64.7% vs. 34.4%), a significantly lower

Table 1. Characteristics of 95 HIV-infected patients.

Parameter	Results
Sex, % (n) Male Female	 80.0 (76) 20.0 (19)
Median age at the time of diagnosis (range, years)	35 (1–216)
Median duration of follow-up (range, months)	50.9 (1–216)
Median duration of HIV infection (range, months)	38 (1–228)
New HIV diagnosis at first admission, n (%)	83.2 (79)
AIDS diagnosis, % (n)	45.3 (43)
Patients on cART, % (n) Median duration of treatment (range, months)	72.6 (69) 34 (1–146)
Opportunistic infections, % (n)	14.7 (14)
Other infections, % (n)	61.1 (58)
Malignancy, % (n)	6.3 (6)
Exitus, % (n)	6.3 (6)

Table 2. Characteristics of 34 HIV-infected patients with thrombocytopenia.

Parameter	Results
Sex, % (n) Male Female	 88.2 (30) 11.8 (4)
Median age at the time of diagnosis (range, years)	37 (16–71)
Thrombocytopenia at first admission, % (n) Thrombocytopenia during follow-up Thrombocytopenia while receiving cART	52.9 (18) 47.1 (16) 35.3 (12)
Isolated thrombocytopenia, % (n) Thrombocytopenia and anemia Thrombocytopenia and neutropenia Pancytopenia	32.4 (11) 20.6 (7) 2.9 (1) 44.1 (15)
Platelet count, % (n) 101,000–150,000/μL 50,000–100,000/μL <50,000/μL	 32.4 (11) 38.2 (13) 29.4 (10)
Duration of thrombocytopenia, % (n) <3 months ≥3 months	 52.9 (18) 47.1 (16)
Bleeding, % (n)	11.8 (4)
Administration of fresh frozen plasma, % (n)	14.7 (5)
Exitus, (%) n	14.7 (5)

Table 3. Comparison of patients with thrombocytopenia (cases) and without thrombocytopenia (controls) regarding continuous variables.

Parameter	Cases, n = 34	Controls, n = 61	P-value
Median age at the time of diagnosis (range, years)	37 (16–64)	38 (24–71)	>0.05
Median duration of follow-up (range, months)	44 (2–216)	33.5 (1–156)	>0.05
Median duration of HIV infection (range, months)	49 (3–218)	34 (1–228)	>0.05
Baseline median CD4+ T lymphocyte count (range, cells/μL)	159 (0–628)	367.5 (11–1380)	<0.05
Baseline median plasma HIV-RNA (range, copies/mL)	42,250 (<20–2,570,000)	40,050 (<20–5,730,000)	>0.05
Baseline median neutrophil count (range, cells/μL)	3260 (385–7980)	3300 (1130–7230)	>0.05
Baseline mean white blood cell count (SD, cells/μL)	5400 (2800)	6300 (1900)	>0.05
Baseline median hemoglobin level (range, g/dL)	12.6 (6.38–17.4)	13.4 (4.5–16.7)	>0.05

Table 4. Comparison of patients with thrombocytopenia (cases) and without thrombocytopenia (controls) regarding categorical variables.

Parameter	Cases (n = 34) % (n)	Controls (n = 61) % (n)	P-value
HBsAg positivity	2.9 (1)	6.5 (4)	> 0.05*
Anti-HCV positivity	14.7 (5)	0.0 (0)	<0.05*
Anti-Delta positivity	2.9 (1)	1.6 (1)	>0.05*
VDRL positivity	8.8 (3)	9.8 (6)	>0.05*
AIDS diagnosis	64.7 (22)	34.4 (21)	<0.05
History of:			
cART usage	38.2 (13)	91.8 (56)	<0.05
Comorbid diseases	67.6 (23)	57.3 (35)	>0.05
Malignancy	8.8 (3)	4.9 (3)	>0.05*
Chemotherapy	5.8 (2)	1.6 (1)	>0.05*
CMV infection	14.7 (5)	3.2 (2)	>0.05*
TMP/SMX prophylaxis	50.0 (17)	29.5 (18)	<0.05
Azithromycin prophylaxis	41.7 (8)	3.2 (9)	>0.05
Fluconazole treatment	20.5 (7)	21.3 (13)	>0.05
Opportunistic infections	42.9 (6)	57.1 (8)	>0.05
Tuberculosis coinfection	17.6 (8)	7.8 (5)	<0.05*
Antituberculosis therapy	20.5 (7)	8.1 (5)	>0.05*

*Fisher's exact test.

number of patients with thrombocytopenia were using or ever had used cART.

Overall, the frequency of thrombocytopenia ranged from 5% to 59% in HIV-infected patients. The rate was higher in patients with AIDS (20% to 59%) than patients without AIDS (5% to 15%) (22,29). Types of the cytopenia may differ according to geographic regions. In a multicenter study, while anemia and neutropenia were more frequent in South Africa, thrombocytopenia was more frequent in Brazil and India (26). The definition of thrombocytopenia differs among studies (18,29). In this study, when all patients were included, the overall rates were 35.8%, 24.2%, and 10.5% for platelet count of <150,000/μL, <100,000/μL, and <50,000/μL, respectively. These rates

were higher than in earlier reports (19,30,31). Differences among studies might be related to the differences in the definition of thrombocytopenia or the heterogeneity of the study population, or racial factors. In our study, low median CD4+ T lymphocyte count at first admission (280 cells/μL), which is consistent with late diagnosis of HIV infection, might be one explanation.

In a multicenter study, the frequency of thrombocytopenia (<125,000/μL) in ART-naive patients was 7.2% (26). In another study, however, even in the era of cART, frequency of thrombocytopenia (platelet count of <150,000/μL) ranged from 9.2% in patients without AIDS to 21.2% in patients with AIDS (18). Similarly, in our study, the frequency of thrombocytopenia was higher in patients with AIDS (51.2%) than patients without AIDS (23.1%).

Studies have shown that the frequency of thrombocytopenia in HIV infection also differs according to sex. The rate was higher in males than females (18,19,26). Regarding age, however, there was no consistency among studies (3,18,31–34). In our study, the 2 groups were similar regarding sex and age.

Many studies showed that thrombocytopenia was more frequent and more severe in patients who were in more advanced stages of HIV infection, or who had lower CD4+ T lymphocyte counts (3,6,18,22,25,31,32,35,36). Regarding the relationship between thrombocytopenia and plasma HIV-RNA levels, however, reports are not consistent (6,25,31,36–38). Similar to these findings, in our study, patients with thrombocytopenia had a significantly lower median CD4+ T lymphocyte count than the control group ($P < 0.05$), but the median plasma HIV-RNA levels were similar between the 2 groups ($P > 0.05$). Consequently, frequency of thrombocytopenia was higher in patients who had used TMP/SMX for the prophylaxis of opportunistic infections because of low CD4+ T lymphocyte counts. Although TMP/SMX can cause thrombocytopenia (20), in none of our patients its use was the cause of thrombocytopenia.

The effect of cART on cytopenias was also evaluated in earlier studies. Overall, the rate of thrombocytopenia was 9.8% in patients on cART for 96 weeks (36). Antiretroviral therapy favorably affected all cytopenias, including thrombocytopenia (37,39), whereas interruption of cART was associated with emergence of thrombocytopenia in several studies (36,40). In our study, similarly, the rate of thrombocytopenia was significantly higher in cART-naive patients than patients on cART. Although cART favorably affected cytopenias, among antiretroviral drugs, delavirdine, didanosine, indinavir, lamivudine, nelfinavir, nevirapine, saquinavir, ritonavir, and zidovudine were associated with thrombocytopenia (24,41). In one of our patients, after all other causes were excluded, the cause of thrombocytopenia was related to didanosine usage.

Although the frequency of thrombocytopenia was associated with the CD4+ T lymphocyte count at first admission, no relationship was found between opportunistic infections in general and thrombocytopenia. When the analysis was repeated specifically for tuberculosis, however, the frequency of thrombocytopenia was significantly higher in patients who either at present or in the past had tuberculosis. Unlike other opportunistic infections, tuberculosis, and especially pulmonary involvement, can be seen in all stages of HIV infection, and in most coinfected patients CD4+ T lymphocyte counts were higher than 500 cells/μL (42). In our cohort, however, coinfected patients with HIV and tuberculosis were in more advanced stages of HIV infection with a median CD4+ T lymphocyte count of 73 cells/μL: (range: 1–686 cells/μL), and this might be the explanation for the association between tuberculosis and thrombocytopenia. Drugs used for the treatment of tuberculosis, namely isoniazid, rifampicin, rifabutin, ethambutol, and ethionamide, can also cause thrombocytopenia (43–46), but in none of our patients was the cause of thrombocytopenia related to antituberculous drugs.

In our study, the frequency of thrombocytopenia was significantly higher in HCV-coinfected patients, and earlier studies also supported this finding (21,25,47). Regarding HBV, however, only 1 study reported hepatitis B surface antigen (HBsAg) positivity as a risk factor for thrombocytopenia in HBV-coinfected patients (26). No association was found in our study.

Reports of the effect of thrombocytopenia on mortality rates in HIV-infected patients differ among studies. Some studies reported higher rates of mortality (3–5), and others did not find a relationship between thrombocytopenia and prognosis of HIV infection (48–50). In our study the mortality rate was higher in patients with thrombocytopenia than without (14.7% vs 1.6%). It was also noteworthy that 5 of the 6 deaths during the study period were in thrombocytopenic patients.

The results of this study should be interpreted within the context of its limitations. The main limitation was the single-center, retrospective design of the study. The results cannot be generalized to all HIV-infected patients. The study power was low and type 2 error was high due to the low sample size. Thus, some differences between the 2 groups might be missed. In addition, multivariate analysis was not performed as the data set was not appropriate. Despite these limitations, in our study, total follow-up duration was 403 patient-years and the comparison of the case and the control groups enabled us to derive

more information than earlier reports of frequencies of thrombocytopenia in different countries. Still, more comprehensive studies are needed in this field.

In conclusion, we found thrombocytopenia in 34 (35.8%) patients. The main finding was the clear association between thrombocytopenia and advanced (low CD4+ T lymphocyte count, AIDS diagnosis, need for TMP/SMX prophylaxis) and uncontrolled (antiretroviral-naive) HIV infection. Tuberculosis and HCV coinfections were also identified as associated factors for thrombocytopenia.

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