

Rheumatic Manifestations in HIV Positive Patients at Soetomo Hospital Indonesia

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Abstract

Background: Rheumatic disease is one of the comorbidities that can occur in patients with Human Immunodeficiency Virus (HIV) infection. The prevalence and the spectrum of the diseases are varied in some previous studies. The emergence of rheumatologic diseases can increase morbidity and decrease the quality of life of HIV-positive patients. **Purpose:** This study aims to determine the variety of rheumatologic diseases that occur in HIV positive patients and the characteristics of the patients. **Methods:** This study is a descriptive study. Data obtained from the medical record of patients include the data sociodemographic, CD4 cell count, and history of antiretroviral drugs as well as the data from patient interviews. This study was carried out on 130 patients with HIV who were controlled at Dr. Soetomo Hospital, Surabaya, in the period of June 2019. **Results:** HIV-positive Patients were dominated by men (66,9%) with a mean age of 37.36 (± 9.524). The patient's average CD4 cell count was 322.95 cells/mm³ ($\pm 145,523$) and the most widely used drug combinations were tenofovir, lamivudine, and efavirenz (66.2%). Rheumatic manifestations were obtained in 25 of 130 (19.2%) with joint pain in 13 (10.0 %) cases, myalgia 4 (3.1%) cases, systemic lupus erythematosus 4 (3.1%) cases, osteomyelitis 2 (1.5%) cases, osteoarthritis 1 (0.8%) case, and spondylarthropathy 1 (0.8%) case. **Conclusion:** Several types of rheumatic manifestations were found in HIV-positive patients with arthralgia being the most common. Rheumatic manifestations commonly occur in adult men with low CD4 cell counts. Early detection and appropriate therapy related to rheumatic manifestations of HIV infection are expected to improve the patient's quality of life.

Keywords: HIV, Rheumatology, Rheumatic Disease, Arthralgia, Myalgia, Systemic lupus erythematosus, Osteoarthritis.

1. Introduction

Human immunodeficiency virus (HIV) infection continues to be a major global health problem that has infected more than 35 million people and continues to increase every year. [1]. Likewise in Indonesia, HIV infection is a serious issue. Cases of HIV infection and AIDS tend to increase every year with various accompanying diseases. This can cause problems for both patients and clinicians [2].

Rheumatic manifestations are one of the comorbidities that appear in HIV-positive patients [3]. Several studies show different prevalence [4, 5, 6]. Rheumatic manifestations that appear also vary. Arthralgia is one of the most frequent manifestations [3]. In addition, myalgia, osteomyelitis, systemic lupus erythematosus (SLE), and rheumatoid arthritis are also common in HIV-positive patients. [5, 6].

There are few studies on rheumatic manifestations in HIV-positive patients in Indonesia. This study aims to determine the prevalence of rheumatic manifestations in HIV-positive patients, especially at Dr. Soetomo Hospital, Surabaya.

2. Methods

2.1. Data collecting

This study is a descriptive study. The population were all HIV-positive patients who had routine check-ups at Dr. Soetomo Hospital, Surabaya. The sample of this study were patients who came for routine check-ups to Dr. Soetomo Hospital in June 2019. The sampling method was consecutive sampling method. The number of samples was 130 patients according to the formula below with α was 5% and the previous prevalence based on a study by Yao et al. [6] was 9%, which shows that the minimum sample was 126 patients

$$n = \frac{Z\alpha^2 X P X Q}{d^2} \quad (1)$$

$$n = \frac{1.96^2 \times 0.09 \times 0.91}{0.05^2} \quad (2)$$

$$n = 125.85 \approx 126 \quad (3)$$

The patients for this study were patients who came for routine check-ups during the period and had met the inclusion-exclusion criteria. The inclusion criteria were adult patients and voluntarily participated in this study. The exclusion criteria is if the data is incomplete

2.2. Data analysis

Collecting patient data through interviews and viewing secondary patient data in medical records. Data collected in the form of age, gender, occupation, use of antiretroviral (ARV), CD4 cell count and rheumatic manifestations of the patient. The data was inputted into Microsoft Excel and each variable was calculated for its frequency, average, standard deviation, minimum and maximum values. Then the data was presented in tables to see the number of rheumatic manifestations and their characteristics.

3. Results

In this study, from 130 patients, there were 87 (66.9%) male patients and 43 (33.1%) female patients. The age range mostly in the 30-39 year range as many as 53 (40.8%) patients followed by the 40-49 year age range as many as 34 (26.2%) patients, 20-29 as many as 26 (20.0%) patients, 50-59 were 14 (10.8%) patients, less than 20 years old were 2 (1.5%) patients, and over 59 years old were 1 (0.8%) patients. The average age of HIV-positive patients was 37.36 years old ($SD \pm 9.524$) with the youngest being 18 years old and the oldest being 60 years old.

The CD4 levels of HIV-positive patients were higher at levels less than 350 cells/mm³ in 72 (55.4%) patients, while the CD4 levels were more than 350 cells/mm³ in 58 (44.6%) patients. The highest CD4 level was 595 cells/mm³ while the lowest was 105 cells/mm³ with an average of 322.95 cells/mm³ ($SD \pm 145.523$). The most widely used ARV options for HIV-positive patients in this study were Lamivudine (3TC) in 130 (33.3%) patients followed by Efavirenz (EFV) in 88 (22.6%) patients, Tenofovir (TDF) in 86 (22.1%) patients, Zidovudine (ZDV) in 44 (11.3%) patients, Nevirapine (NVP) in 41 (10.5%) patients, and Lopinavir/Ritonavir (LPV/r) in 1 (0.3%) patients. The most widely used combination of ARVs is a combination of TDF, 3TC and EFV in the form of a fixed dose combination.

It was found that 25 (19.2%) HIV-positive patients had rheumatic manifestations or diseases. The various rheumatic manifestations are as presented in table 1 while the patient characteristics are in table 2. The most common rheumatic manifestations in this study were arthralgia in 13 (10.0%) patients. Other manifestations were myalgia in 4 (3.1%) patients, SLE in 4 (3.1%) patients, osteomyelitis in 2 (1.5%) patients, osteoarthritis in 1 (0.8%), and spondyloarthropathy in 1 (0.8%) patient.

Table 1. Rheumatic Manifestations in HIV-positive Patients at Dr. Soetomo Hospital.

Rheumatic Manifestations	Number (%)
Arthralgia	13 (10.0%)
Myalgia	4 (3.1%)
Osteoarthritis	1 (0.8%)
Osteomyelitis	2 (1.5%)
Systemic lupus erythematosus	4 (3.1%)
Spondyloarthropathy	1 (0.8%)
Total	25 (19.2%)

Table 2. Characteristics of HIV-positive Patients with Rheumatic Manifestations at Dr. Soetomo Hospital.

Variable	Arthralgia	Myalgia	Osteoarthritis	Osteomyelitis	SLE	Spondyloarthro- pathy	Total
Gender							
Male	8	3	1	2	1	1	16 (64.0%)
Female	5	1	-	-	3	-	9 (36.0%)
Age							
20-29	1	1	-	1	3	-	6 (24.0%)

30-39	4	1	-	1	-	1	7 (28.0%)
40-49	5	2	1	-	1	-	9 (36.0%)
50-59	3	-	-	-	-	-	3 (12.0%)
CD4 Count							
<350	9	3	-	1	3	1	17 (68.0%)
≥350	4	1	1	1	1	-	8 (32.0%)
Antiretroviral drugs							
TDF+3TC+EFV	9	3	-	2	4	1	19 (76.0%)
ZDV+3TC+NVP	3	1	1	-	-	-	5 (20.0%)
ZDV+3TC+EFV	1	-	-	-	-	-	1 (4.0%)

*TDF = Tenofovir; 3TC = Lamivudine; EFV = Efavirenz; ZDV = Zidovudine; NVP = Nevirapine

4. Discussions

In this study, 25 (19.2%) of the 130 HIV patients had rheumatic manifestations. This prevalence is higher than the study by Yao et al [6] in New Jersey, USA, where the prevalence of rheumatic disease was 9%. However, other studies have a higher prevalence. Research in Uganda found 81 (27%) rheumatic manifestations [3]. Research by Azami et al. [7] in Iran showed 63 (31.5%) cases of rheumatic manifestations. Research by Chiowchanwisawakit et al. [4] in Thailand found 98 (55%) cases of rheumatic. Research by Kole et al. [5] in India showed 190 (63.3%) cases of rheumatism. Table 3 shows some comparisons of the spectrum of rheumatic manifestations in HIV patients

Table 3. Comparison of the Prevalence of Manifestations in HIV-positive patients (%)

Rheumatic manifestations	Chiowchanwisawakit et al. (2005)	Kole et al. (2013)	Yao et al. (2008)	Azami et al. (2012)	This study
Arthralgia	13.5	26.7	5.5	12.5	10.0
Myalgia	10.1	46.7	-	3.5	3.1
Osteoarthritis	-	6.0	-	-	0.8
SLE	-	0.3	0.3	-	3.1
Spondyloarthropathies	-	0.7	-	2.0	0.8
Osteomyelitis	-	0.3	0.9	-	1.5

Arthralgia was the most common manifestation in this study. Likewise research by Azami et al. [7] and Yao et al. [6] showed that arthralgia was also the most common manifestation. The prevalence of HIV-positive patients with arthralgia manifestations was found to be more male (61.5%) with an average age of 42.54 years old ($SD \pm 10.413$) and an average CD4 cell count of 309.85 cells/mm³ ($SD \pm 141.490$). However, there are many differences in prevalence in each study. In general, clinical joint pain that occurs is mild, intermittent, and often attacks the knees, shoulders, and elbows [8]. The pathogenesis of this problem is still unclear. It is possible that cytokines play a role in these manifestations [9] or due to bone edema due to increased avascular necrosis [10].

Myalgia is one of the most common clinical manifestations in HIV patients. The research of Kole et al. [5] showed myalgia as the most common manifestation with a prevalence of 46.7%. In this study, myalgia was the second most common manifestation (3.1%). Myalgia was found more in males (75.0%) with a mean age of 35.00 years old ($SD \pm 9.129$) and the majority received tenofovir-lamivudine-efavirenz therapy (75.0%). Another study showed an increase in cases of myalgia since the use of combination antiretroviral therapy [11]. The use of Zidovudine has a role in cases of myopathy which can cause myalgia and muscle weakness manifestations [12]. However, stopping Zidovudine is not always successful in treating the pain [8].

In this study, one (0.8%) patient had osteoarthritis, male, 49 years old, and receiving combination therapy with zidovudine-lamivudine-nevirapine. These results are similar to the study by Tomi et al. [14] showed that the majority of patients with osteoarthritis were male with a mean age of 53.4 years old. HIV positive patients may develop osteoarthritis earlier and are more aggressive than the general population [14]. The use of ARVs may increase the degeneration of the knee cartilage matrix. In addition, HIV positive patients may develop significantly more severe joint effusions than HIV negative patients [15].

The prevalence of osteomyelitis was 1.5% (2 male patients) in this study, with an average age of 28 years old and a CD4 cell count of 343 cells/mm³. Osteomyelitis is one of the most common manifestations of musculoskeletal infection in HIV-positive patients [16] and according to Tehranzadeh et al. [17], this case mostly affects young men. *Staphylococcus aureus* is the most common cause of osteomyelitis in both HIV-positive patients and the general population, but HIV-positive patients are also at risk for rare pathogens, such as *Salmonella*, *Mycobacteria* (especially *M. tuberculosis*), *Cryptococcus*, *Candida*, or *Cytomegalovirus* [18]. According to Tehranzadeh et al. [17], the most common sites are the wrist, tibia, femoral head, and thorax. However, since the era of combination antiretroviral therapy, osteomyelitis and musculoskeletal infections have become less common [10].

There were 4 SLE cases in HIV-positive patients in this study (3 women and 1 man) with an average age of 30.75 years old. These results are similar to the study of Fox and Walker-Bone [11] that the age of SLE patients with HIV infection is around 30 years old with 70% of cases in women. HIV-infected SLE patients have seen a decrease in the incidence of disease symptoms [19]. However, the administration of combination therapy can significantly trigger a recurrence of SLE with rash and transverse myelitis manifestations [20]. In some cases, SLE was diagnosed later after being infected with HIV. This may be due to retroviruses that produce auto-antibodies or due to HIV infection that inhibits SLE conditions leading to late diagnosis [11]. The cases of SLE that appear after HIV infection are caused not only by genetics but also by environmental factors [21].

In this study, there was one HIV-positive patient with manifestations of spondyloarthropathies (male, 38 years old). The patient's CD4 count was low at 111 cells/mm³. The combination therapy used by the patient was tenofovir-lamivudine-efavirenz. Kole et al. [5] obtained similar results with a prevalence of spondyloarthropathies of 0.7%. The incidence of spondyloarthropathies was significant in HIV-positive patients who were not taking combination antiretroviral therapy. The emergence of HIV led to changes in the epidemiology of spondyloarthropathies. In sub-Saharan Africa, spondyloarthropathies have increased since the HIV epidemic [22]. In addition, HIV infection may also increase the severity of spondyloarthropathies and psoriasis [23]. According to McGonagle et al. [24], there are three pathogenic mechanisms that may contribute to disease severity include increased exposure to infectious agents, an adequate CD8 T cell repertoire, and biomechanical factors that play a role in localization of primary disease. According to Reveille and Williams [26] effective use of ARVs can improve the symptoms of the disease.

5. Conclusion

Rheumatic manifestations may occur in HIV-positive patients but are uncommon. Manifestations that appear have a broad spectrum ranging from arthralgia, myalgia, osteoarthritis, osteomyelitis, systemic lupus erythematosus, to spondyloarthropathies. The Characteristics of HIV-positive patients with rheumatic manifestations are generally dominated by men with slightly low CD4 cell counts and using combination ARV therapy. It is hoped that this study can increase clinicians' awareness of rheumatic manifestations in HIV-positive patients.

6. Recommendations

This study still has some limitations and the researcher suggests that a study with a larger and wider sample is needed in order to obtain more representative results and also further research is needed to see the association of patient characteristics and the emergence of rheumatic diseases.

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