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Pansitopenia as a Marker of Advanced Human Immunodeficiency Virus (HIV) infection: How Often? A Case Study Accompanied by Literature

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ABSTRACT

Pansitopenia is a condition characterized by anemia, thrombocytopenia, and leukopenia. One of the common etiologies of Pansitopenia is HIV infection. In advanced HIV, Pansitopenia may present even without other clinical findings leading to a diagnosis of HIV. This study was conducted as a case study of a 34-year-old man who presented with chief complaints of chronic diarrhea and fever that lasted for one month. Laboratory examination showed Pansitopenia, HIV-rapid reactive and peripheral blood picture indicating Pansitopenia/ aplastic anemia. Data were collected through history taking, physical examination, and a series of laboratory tests. The patient was diagnosed with Pansitopenia suspected to be caused by HIV infection. The chief complaints of chronic diarrhea and fever suggested a chronic disease process due to immune compromise, as seen in the patient's clinical status indicating advanced HIV. The literature suggests that the severity of pansitopenia depends on the severity of HIV disease. Pansitopenia can be an indicator of the advanced stage of HIV infection. Appropriate management and regular monitoring are essential to prevent further complications. Pansitopenia in HIV patients can be considered as an important indicator to assess the severity of the infection. Prompt treatment and antiretroviral therapy are highly recommended to improve the prognosis of patients.

Keywords: chronic diarrhea, pansitopenia, aplastic anemia, Human Immunodeficiency Virus (HIV)

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INTRODUCTION

Pansitopenia can be defined by a hematological condition characterized by a decrease in all three blood lines, either hemoglobin values ≤ 12 gr/dL in women and ≤ 13 gr/dL in men, platelet values ≤ 150,000/uL, and leukocytes ≤ 4,000/uL (or absolute neutrophil count ≤ 1,800/uL). These threshold values depend on age, gender, race and various clinical scenarios. Pansitopenia itself is not a disease, but a manifestation of another underlying condition/ etiology (Shalini C, 2023). The causes of Pansitopenia can largely be categorized into disorders of peripheral cell damage, or impaired bone marrow production. However, most conditions tend to exhibit characteristics of both, as Pansitopenia can arise from a variety of different pathophysiological mechanisms. These causes can lead to Pansitopenia separately or in combination (Priyanto & Mas'ud, 2024). The morbidity and mortality of Pansitopenia depend on the underlying etiology. The most common etiologies are the effects of chemotherapy, Human Immunodeficiency Virus (HIV) infection, infiltration or failure of the bone marrow. Thus in some cases, Pansitopenia can only be definitively diagnosed by bone marrow aspiration and trephine biopsy (Chew & Kamangar, 2024).

Human Immunodeficiency Virus (HIV) disease is defined as a virus that attacks the human immune system and causes a state of CD4 lymphopenia resulting in decreased general immune activation, which then leads to opportunistic infections and neoplasms, and can eventually fall into the condition of Acquired Immune Deficiency Syndrome (AIDS) (De Torres et al., 2021; Hossain et al., 2022). HIV is a lentivirus, a subgroup of retroviruses, a single-stranded RNA virus. The virus is found and transmitted through body fluids, especially blood, semen, vaginal fluids and breast milk (Aresta & Jumaiyah, 2019; Pudjiati et al., 2019). HIV can

be classified into types 1 and 2 (HIV-1, HIV-2) (Blood, 2016). Proper diagnosis between HIV-1 and HIV-2 is very important because there are clear differences in response to antiretroviral therapy (Armstrong et al., 2016). According to WHO data on HIV, there will be 39 million patients with HIV by the end of 2022. This is an increase from 37.7 million cases at the beginning of 2022 (Harini & Susanti, 2017; Isni & Matahari, 2018; Surahmawati & Faisal, 2023). The number of people living with HIV (PLHIV) in Indonesia in 2020 was 543,100, with the most causes (28.8%) due to injection drug use and followed by male-to-male sex (25.8%) (Arifin et al., 2023).

Data from the Ministry of Health suggests that by 2020, there will be approximately 543,100 people living with HIV, and the infection is often accompanied by hematology-related symptoms. Research by Fitriani et al. (2023) revealed that Pansitopenia can be an indicator of advanced HIV infection, and hospital cases show that patients with Pansitopenia often do not receive antiretroviral treatment, which contributes to a worse prognosis.

Diagnosis of HIV begins with a systematic history and physical examination of the suspected HIV patient. In addition to characterizing symptoms, the history can identify risk factors for HIV transmission such as sexual contact and behavior, drug use, blood transfusion. Antibody, antigen-antibody and nucleic acid amplification testing can be used to screen or confirm HIV in the symptomatic phase of disease. There are no currently available testing technologies that can detect HIV during the early viremia phase of infection, known as the window period. In Indonesia, HIV diagnosis can be established using 2 testing methods, namely serological and virological testing. Serological testing methods using antibodies and antigens, for example: rapid immunochromatography test, and EIA (Enzyme Immunoassay). While the virological examination method, namely HIV DNA and HIV RNA examination, is used for HIV diagnosis in infants, and only exists in a few places. HIV test results are said to be positive if 3 serological examination results with three different methods or reagents show reactive results, or quantitative or qualitative virological examination detected the HIV virus (Bukhori et al., 2022).

The appearance of Pansitopenia in HIV patients is not only a clinical sign, but may also indicate that HIV infection has reached an advanced stage. This study aims to explore the relationship between Pansitopenia and HIV infection, and review relevant literature to support these findings.

METHOD

a. Study Design

This study was a case study conducted to evaluate the relationship between Pansitopenia and HIV infection in patients. Data were collected through observation and analysis of relevant literature.

b. Study Subject

The study subject was a 34-year-old man who came to the hospital with complaints of chronic diarrhea and fever that lasted for one month. Medical history showed that the patient had been diagnosed with HIV one year earlier but was not on treatment.

c. Data Collection

Data was collected through the following steps:

1. **Anamnesis**: Collect information regarding the patient's medical history, including chief complaint and history of HIV infection.
2. **Physical Examination**: Conduct a physical examination to assess vital signs and clinical symptoms.
3. **Laboratory Examination**: Perform a series of blood tests to assess anemia, leukopenia, and thrombocytopenia. These tests include:
    - Complete blood count
    - Rapid HIV test
    - Additional tests to assess kidney function and other possible infections.

4. **Literature** review: Conduct a literature review of 5 relevant previous studies to identify patterns and associations between Pansitopenia and HIV infection.

d. Data Analysis.

Data obtained from clinical and laboratory examinations were analyzed to determine the association between Pansitopenia and the severity of HIV infection. Findings from literature studies were also analyzed to support or refute the results obtained from this case study.

RESULTS AND DISCUSSION

In this case, a 34-year-old man was examined, with a chief complaint of liquid bowel movements experienced since 1 month, and aggravated since approximately 8 days ago. Defecation >5 times a day, not mucous, not bloody, pulp is still present. The patient also complained of weakness. Fever has also been experienced by the patient since approximately 1 month, up and down indefinitely. Coughing cold is denied, shortness of breath is denied. The patient is difficult to communicate, it has been a long time, the patient often daydreams and must be repeated when invited to communicate. Eating and drinking are difficult. There is weight loss, but the exact number is unknown. The patient has had mouth ulcers since the last few weeks, and the ulcers have appeared and disappeared. In the history of previous illnesses, after reanamnesis, the patient said honestly that he had been diagnosed with HIV about 1 year ago, but did not want to seek treatment. According to the confession, the patient is not married, but has changed partners several times and had sex with the last comfort woman about 1 year ago. The patient worked as a fisherman. Physical examination, the patient had a fever with a body temperature of 39.2 degrees Celsius. The lungs were found to have pulmonary rhonki but without complaints of coughing.

Diarrhea is a common disease and causes more than one million deaths annually worldwide. If symptoms persist for more than four weeks, the condition is known as chronic diarrhea, which occurs in 5% of the population under certain conditions. It can be fatal in patients with weakened immune systems and the incidence rate is at least 10 times higher in individuals infected with the *Human Immunodeficiency Virus* (HIV), compared to the general population. Diarrhea can affect HIV patients at any stage of the disease and up to 60% of patients with HIV report experiencing symptoms of diarrhea. Despite antiretroviral therapy (ART), HIV-associated diarrhea still has multifactorial causes including infectious processes, neoplasia, and eneteropathy, leading to altered quality of life, failure of antiretroviral treatment adherence, weight loss, and malnutrition.

This is similar to what was revealed by Mahayani NPO et al in a study at Sanglah Hospital in Denpasar, where 49 research subjects with diagnosed HIV were found as many as 22 subjects had experienced diarrhea in the first 1 year of HIV diagnosis. And 10 of the 22 patients were at stage III HIV and 14 patients suffered from malnutrition. Of the 22 patients, 10 patients who despite using ARVs, but still experience diarrhea. Supporting examinations were carried out at the Emergency Department (ED). Supporting tests aimed to point to the underlying cause of the patient's main complaint (Table 1).

Table 1. Supporting examination

Support Name	Date	Results
Blood lab	8/10/2024	Anemia (6.3) (normal = 13.2-17.3gr/dL) Leukopenia (1,570) (normal = 3,800-10,600/uL) Thrombocytopenia (80,000) (normal = 150,000-450,000/uL) Ureum (100.6) (normal = 10-50mg/dL) Creatinine (1.7) (normal 0.6-1.0mg/dL) HIV rapid (reactive) (normal = non-reactive)
ECG	8/10/2024	sinus tachycardia, with a *heart rate of* 115 x/min.
Thoracic X-ray	8/10/2024	impression of cast not enlarged, picture of bronchopneumonia,

Support Name	Date	Results
Edge Blood Picture	8/10/2024	suspicious of *underlying* TB Pansitopenia DD/ 1) *aplastic anemia ec acquired aplastic anemia*, DD: - *viral infection*; - *drug induced ec dose dependent*; 2) *Myelodysplastic Syndrome*; 3) Pansitopenia *other caused*

In this patient, the history and physical examination suspected a chronic infection which prompted a *rapid diagnostic test* for HIV and reactive results, as well as peripheral blood morphology suggesting possible aplastic anemia. The patient was diagnosed with Pansitopenia with HIV infection as the most likely etiology.

Most HIV-infected people are asymptomatic at the onset of HIV infection, with some showing flu-like symptoms within a month or two of infection. These symptoms usually disappear within 1-4 weeks and are often confused with symptoms of other viral infections. This period is called the latent period. After the latent period occurs, the AIDS state will arise which is characterized by weight loss of more than 10% in 1 month, chronic diarrhea and fever for more than 1 month. According to WHO, based on the diagnosis from the history and physical and supporting examinations performed, the likely course of this patient is clinical stage 3 HIV disease. As the disease progresses, additional clinical manifestations may appear. Which falls under the WHO clinical stage 3 category (stage with moderate symptoms). Stage 3 (moderate symptoms) is characterized by unexplained weight loss (>10% of estimated or measured body weight), unexplained chronic diarrhea for more than 1 month, unexplained persistent fever (intermittent or constant for more than 1 month), then infections such as persistent oral candidiasis, pulmonary tuberculosis, severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infections, meningitis, bacteremia), ulcerative stomatitis, gingivitis or periodontitis. And what can also occur is unexplained anemia (<8 gr/dL), followed by neutropenia (<0.5 × $10^{9/}$ L) and/or chronic thrombocytopenia (<50 × $10^{9/}$ L), which if all three occur is called Pansitopenia.

The suspicion of a chronic disease process, possibly caused by immunocompromise, resulted in opportunistic infections in this patient. This is due to the decrease in CD4+ T lymphocytes that are attacked and destroyed by the HIV virus, which describes the immunological status and degree of immune suppression.[19] This patient also had Pansitopenia. The etiology of Pansitopenia can be broadly categorized as central type involving impaired production or peripheral type involving increased destruction. One of the causes of Pansitopenia is bone marrow failure known as aplastic anemia which can be caused by infection such as HIV infection in this case. In addition to a strong suspicion towards production disorders, the HIV virus can cause splenic sequestration which also causes Pansitopenia.

Here are some studies related to the prevalence of Pansitopenia in patients with HIV disease:

1. Research by Eduardo JSR *et al* (2015) in a study entitled "Profile of HIV-infected Hispanics with Pansitopenia" found, of 1202 patients with Pansitopenia, 41% of subjects had CD4 <200 cells/ul, 8.6% showed clinical AIDS and 62% were ART recipients. In patients with HIV alone, only 105 patients (8.7%) showed Pansitopenia, however, in general, more than half of the patients (54.5%) had at least one cytopenia. Several studies have shown that cytopenias tend to occur in patients with advanced HIV infection.
2. Research by Sandra RL *et al* (2022), with the title "*HIV-Positive Patients Presenting With Peripheral Blood Cytopenias: Is Bone Marrow Assessment A Priority?"*, which examined 236 incidents of cytopenia in patients with HIV / AIDS (PLWHA). A total of 47.9% were PLWHA who had a long-standing diagnosis (≥ 1 year) with antiretroviral adherence of 63.5%. Anemia was seen in 91.9% of the total study patients and Pansitopenia in 39% of the total study patients. At the time of antiretroviral therapy (ART), anemia has been described as the main cytopenia reported in approximately 50%, followed by leukopenia and thrombocytopenia. Cytopenic events, especially if severe, have been associated with

advanced stage of disease, increased disease progression, and decreased overall survival in PLWHA.

3. Research in Indonesia conducted by Fitriani et al (2023) which examined the relationship between Pansitopenia with CD4 cells on the severity of HIV / AIDS in HIV Naive patients at RSUD dr. Saiful Anwar Malang, obtained the results of 38 patients of research subjects that there was no relationship between Pansitopenia with CD4 cells and with the severity of HIV clinical stages in HIV / AIDS patients. This is due to multifactors, including the number of samples and clinical deepening of each subject. CD4 count may be more meaningful than clinical stage with the association of Pansitopenia in HIV/AIDS patients, because the CD4 factor is more specific and definite than clinical stage.
4. Research by Lina F *et al* (2020) entitled "*Prevalence and Risk Factors of Cytopenia in HIV-Infected Patients before and after the Initiation of HAART"*, and obtained the results of the prevalence of cytopenia was 19.1% in HIV-naive patients (people with HIV who have not undergone ART). Risk factors for cytopenia in HAART-naive patients were CD4 cell count <200 cells/uL, female sex, WHO stage IV, co-infection with hepatitis B virus (HBV), BMI <18.5 kg/m^2 , *viral load* ≥100,000 copies/ml, and age ≥40 years. In total, 70.2% and 76.4% of patients with cytopenia recovered after 6 and 24 months of HAART use, respectively. The predictors of patients with normal blood cells remaining abnormal after 24 months of HAART were the same as risk factors for cytopenias in HIV patients such as CD4 cell count <200 cells/uL.
5. Research by Angesom G *et al* (2020) with the title "*Prevalence of Cytopenia and Its Associated Factors among HIV Infected Adults on Highly Active Antiretroviral Therapy at Mehal Meda Hospital, North Shewa Zone, Ethiopia*", which examined 499 adult HIV cases by getting HAART for at least 6 months and experiencing cytopenia. Of the total study participants, 39.9% had at least one form of cytopenia, 23.2% had anemia, 13.8% had leukopenia, 12.4% had thrombocytopenia, 11.62% had bi-cytopenia, and only 1% had Pansitopenia. In multivariate analysis, cytopenia was independently associated with older age group, male gender, ZDV-based regimen, and CD4 count less than 200 cells/mm.

Of the 5 literature studies, 4 of them mentioned that Pansitopenia indicates advanced clinical stage of HIV disease infection according to WHO, while 1 study conducted in Indonesia showed that it is better to use CD4 count rather than advanced clinical stage to see if Pansitopenia is significantly associated in patients with HIV. The percentages that emerged from the exposure ranged from 1% of 499 cases, 39% of 236 cases, and 8.7% of 1202 cases. And almost all showed that Pansitopenia can be associated with HIV disease that has entered the advanced clinical stage according to WHO. Pansitopenia is a sign of HIV disease, and is reciprocally related. Where when HIV occurs, Pansitopenia can be suspected (some even say it almost certainly causes cytopenia) and when Pansitopenia occurs, we can suspect HIV infection. The severity of cytopenia depends on the severity of the underlying disease, which means it depends on the severity of HIV disease (clinical stage). The severity of cytopenia/Pansitopenia may be a marker of the advanced/end stage of HIV infection. However, it takes more than just clinical manifestations such as viral load or CD4 counts to more accurately determine the severity/stage of HIV.

The therapy obtained by this patient includes infusion of NaCl 0.9% versus Aminofluid (2:1), Levofloxacin injection 500mg/24 hours, Ranitidine injection 1 amp/12 hours, Paracetamol infusion 500mg/6 hours, Dexamethasone injection ½ amp/12 hours, PRC transfusion 4 kolf with extra furosemide 1 amp/kolf if the tension is normal, Install NGT, 6x150cc liquid diet, Per oral enistin 3x10 drops, per oral tab cotrimoxazol 1x960mg, per oral tab loperamide 3x1 tab (if diarrhea), And administration of TLE on the 5th day of treatment after complaints of diarrhea and fever are absent.

Treatment in this case is focused on Pansitopenia and mainly HIV infection. For Pansitopenia, one can start by correcting nutritional deficiencies. Any interfering medications should be discontinued. Treatment for infections such as HIV or tuberculosis should be started

immediately. If autoimmune conditions or malignancies are diagnosed, they should be treated. Supportive care for patients includes red blood cell transfusions for anemia to alleviate symptoms and improve perfusion. Platelet transfusion is indicated for thrombocytopenia of less than 10,000/uL to prevent spontaneous intracranial bleeding. Immediate initiation of broad-spectrum antibiotic therapy is recommended for patients with febrile neutropenia or severe neutropenia with an absolute neutrophil count of less than 500/ ml due to the risk of death from sepsis.

For co-morbidities where the underlying etiology is suspected, HIV needs to be treated. Treatment following exposure of an individual to HIV infection is Antiretroviral therapy (ART) (MD, 2021; Montejano et al., 2019). In addition to treatment for HIV, prophylactic administration of low-dose trimethoprim/sulfamethoxazole (cotrimoxazole) is recommended, as in this case, which provides prophylaxis against cerebral toxoplasmosis, bacterial infections, and malaria in endemic areas. The administration of ARVs in this patient is in accordance with PNPK for HIV. That is using the first line, with TLE or TLD. *Fixed Drug Combination* (FDC) in Indonesia has two options, namely TLD (TDF+3TC+DTG (Tenofovir 300mg+Lamivudine 300mg+Dolutegravir 50mg)), or TLE (TDF+3TC+EFV (Tenofovir 300mg+Lamivudine 300mg+Efivarenz 600mg)). WHO guidelines report that the emergence of new or recurrent WHO clinical stage 3 and 4 conditions after 24 weeks after initiation of therapy indicates treatment failure.

The prognosis of Pansitopenia depends on the underlying condition. Identification of the underlying cause is crucial in managing Pansitopenia. Evaluation of Pansitopenia requires a holistic approach due to the varied etiopathological factors. The prognosis of HIV patients with Pansitopenia is dependent on them not receiving ART, with prognosis worsening after one year without ART treatment. The use of ART in patients with Pansitopenia can reduce their mortality to levels comparable to patients without HIV infection (Santiago-Rodríguez et al., 2016). Hematological abnormalities such as anemia, thrombocytopenia, or leukopenia, or even all three (Pansitopenia) in patients already diagnosed with HIV can be good clinical indicators to predict and assess the underlying immune status. Pansitopenia in patients with HIV indicates advanced HIV infection and is a marker of unfavorable prognosis, as it is associated with medical complications and reduced survival.

CONCLUSION

A 34-year-old man with a chief complaint of chronic diarrhea and prolonged fever with Pansitopenia was reported. Rapid HIV testing with reactive results along with a history of sexual partner changes showed that the patient was indicated / diagnosed as a person with HIV AIDS (PLWHA) with stage 3 or 4 according to the clinical manifestations obtained. The author presents 5 literature studies and shows that patients with HIV generally experience a state of cytopenia, and when Pansitopenia occurs, it indicates that HIV infection has reached an advanced stage or even AIDS. Treatment in our patient was in accordance with PNPK with supportive for Pansitopenia and to treat the etiology (HIV) with the use of first-line FDC in the form of TLE. Monitoring the use of drugs and reactions from therapy needs to be done especially clinically and immunologically to see the effectiveness and prevent drug resistance.

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