Emergency immune reconstitution inflammatory syndrome (IRIS) in HIV drug discontinued with tuberculous meningoencephalitis: a case report

Retnaningsih1*, Muchlis Achsan Udji2, Danar Dwi Anandika3

ABSTRACT

Background: Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical condition in which the administration of ART (antiretroviral therapy) to human immune virus (HIV) patients causes a deterioration in clinical situations. This article describes IRIS in an HIV patient who discontinued the drugs and was accompanied by opportunistic infection with tuberculous meningoencephalitis.

Case Presentation: A 40-year-old male complained of high fever and severe headache for 1 week, then the patient had general tonic-clonic seizures twice and less than 5 minutes. After seizure, patient experiences a deterioration in clinical condition. He had ARDS, respiratory failure and was intubated, but failed resuscitation attempts.

Cerebrospinal fluid (CSF) examination showed 172.8 mg/dL protein, 23 mg/dL glucose, MN 13/mm3, supporting tuberculous meningoencephalitis (METB). Multi sliced CT-Scan (MSCT) head contrast shows enhancement of the basal cistern. The patient received the ART tenofovir-lamivudine-efavirenz. Then he has experienced a decrease in plasma viral load, an increase of CD4 T-cells, which is characteristic of ART to HIV/AIDS patients will lead to Combined immunosuppression in the form of opportunistic infections and neoplasms. When HIV patients have an opportunistic infection, they should begin ART no later than 2 weeks. Administration of ART to HIV/AIDS patients will lead to a decrease in plasma viral load, an increase of the cellular response) are reduced, leading to opportunistic infections and malignancies.

Acquired Immuno Deficiency Syndrome (AIDS) is a collection of symptoms, infections, and conditions. It is caused directly by HIV itself, and (b) Secondary/indirect complications as a result of Combined immunosuppression in the form of opportunistic infections and neoplasms. Neurological disorders arising from opportunistic infections due to HIV depend on the localization of the neuroanatomies involved. Opportunistic infections and neoplasms of the CNS associated with HIV infection generally occur when severe immunodeficiency is present (CD4 lymphocyte count <200 cells/mm3).

When HIV patients have an opportunistic infection, they should begin ART no later than 2 weeks. Administration of ART to HIV/AIDS patients will lead to a decrease in plasma viral load, an increase in inflammatory stage, manifested by hypergammaglobulinemia and increased secretion of several cytokines. A variety of neurological complications, particularly those occurring before the onset of AIDS, are caused by immune-mediated processes. Without control of the virus, even all immune system components (especially neuroanatomies involved). Opportunistic infections and neoplasms of the CNS associated with HIV infection generally occur when severe immunodeficiency is present (CD4 lymphocyte count <200 cells/mm3).

When HIV patients have an opportunistic infection, they should begin ART no later than 2 weeks. Administration of ART to HIV/AIDS patients will lead to a decrease in plasma viral load, an increase in inflammatory stage, manifested by hypergammaglobulinemia and increased secretion of several cytokines. A variety of neurological complications, particularly those occurring before the onset of AIDS, are caused by immune-mediated processes. Without control of the virus, even all immune system components (especially

INTRODUCTION

HIV (Human Immunodeficiency Virus) is a retrovirus in the Lentivirus subfamily, has a long latency period between primary infection and reduced number of CD4 T-cells, which is characteristic of AIDS. During the latency period, the immune system becomes disorganized and progresses to a chronic pro-inflammatory stage, manifested by hypergammaglobulinemia and increased secretion of several cytokines. A variety of neurological complications, particularly those occurring before the onset of AIDS, are caused by immune-mediated processes. Without control of the virus, even all immune system components (especially

1Neurology Department, Faculty of Medicine, Universitas Diponegoro-Dr Kariadi Hospital, Semarang, Indonesia.
2Residency in Neurology Program, Faculty of Medicine, Universitas Diponegoro-Dr Kariadi Hospital, Semarang, Indonesia.
3Internal Medicine Department, Faculty of Medicine, Universitas Diponegoro-Dr Kariadi Hospital, Semarang, Indonesia.
4*Corresponding author: Retnaningsih; Neurology Department, Faculty of Medicine, Universitas Diponegoro-Dr Kariadi Hospital, Semarang, Indonesia; retnaku_icu@yahoo.com

Keywords: antiretroviral, immune response, tuberculosis, meningitis.

in CD4 count, and improve overall immune function. These immunological changes are associated with a decreased frequency of opportunistic infections and an extended patient life span. However, some groups of patients experience deterioration in clinical condition due to dysregulation of rapid repair of specific antigen immune responses during treatment. ART initiation have the possibility of developing immune reconstitution inflammatory syndrome (IRIS), a potentially severe complication that reflects an overaction of the pathogen-specific immunity, caused by immune reconstitution. IRIS is thought to occur after recovery of the adaptive immune system, leading to a hyperinflammatory response to a previously acquired opportunistic infection.

IRIS affects about 10-32% of HIV patients. It can be classified into two different types, paradoxical IRIS and unmasking IRIS. Paradoxical IRIS involves a previously detected opportunistic infection that worsens after ART initiation. Unmasking IRIS occurs in a patient with subclinical opportunistic infection that worsens with recovered immune response after ART. Both of them associated with increased mortality rate.

Here we present a case with drug discontinued in HIV patient accompanied with tuberculous meningoencephalitis, which showed severe deterioration after ART onset and raised the possibility of suffering from IRIS.

**CASE PRESENTATION**

A 40-year-old man complained of high fever for approximately 1 week, he also complained headaches. Previously, he often complained of headaches but was ignored by himself. The weakness of limbs, sensory disturbances, cognitive deterioration, and vomiting are denied. He went to a general practitioner, but there was no significant improvement. The complaint was getting worse within the last couple of day. The patient experienced tonic-clonic seizure, with duration less than 5 minutes and occurred twice while at home. After the seizure, he was unconscious, even until he was brought to the ER. He can only respond to pain stimuli. From the alloanamnesa, he had been diagnosed with HIV 3 years ago, but only took ART for 2 months from the time he was diagnosed with HIV, then discontinued treatment.

Examination: blood pressure 121/87 mmHg, heart rate 104 x/minute, respiratory rate 20 x/minute, temperature 38°C, saturation 100% with NRM 8 litre per minute. Found positive meningeal excitability sign. There were neck stiffness, Brudzinski I, and Kernig’s test. Also found an impression of lateralization to the right side as well as oral candidiasis in patients.

From the laboratory when the patient entering ER found haemoglobin 11.6 g/dL, leucocytes 7,800 /µL, platelet counts 442,000 /µL, urea 61 mg/dL, creatinine 1.18 mg/dL, SGOT 82 µ/L, SGPT 87 µ/L, prokalsitonin 0,19 ng/mL, CRP kuantitatif 2.24 mg/dL.

AP Chest X-Ray examination within normal limits. Electrocardiography normal sinus rhythm impression. From head CT contrast showed a little enhancement in cisterna basalis, give the impression of tuberculous meningoencephalitis. Can be seen in the figure 1.

HIV RNA was detected and the level of CD4 was 65 cells/mm³. CSF examination from lumbal punctae leads to tuberculous infection. Can be seen in table 1.

The patient received vancomycin injection therapy 1 gram/12 hours, micafungin injection 100 mg/24 hours at the beginning of admission to the ER. ART was given to patients after re-screening of HIV RNA positive, namely tenofovir-lamivudine-efavirenz 1 tablet/24 hours. We also performed TB TCM screening procedure and CSF culture. One day after given ART, the patient experienced a decline in consciousness and clinical deterioration. The patient does not respond to pain stimuli more. There was hypotension, desaturation, accompanied by an increase in heart rate >100x / minute. The patient’s pupil appears mydriasis with negative light reflex. Resuscitation...
Risk factors for IRIS have been associated with increased susceptibility to the development of opportunistic infection at the time of ART initiation, making conclusions regarding the study populations and the type of IRIS included in clinical stage IV based on the severity of HIV-AIDS infection according to WHO provisions. Meanwhile, the very low CD4 results indicate a very severe state of immunodeficiency in the patient.

There are several risk factors for the development of IRIS identified, shown in Table 2. Risk factors for IRIS have been investigated in many studies; however, the cohort differs substantially regarding the study populations and the type of IRIS examined, making conclusions regarding risk factors for IRIS difficult. The presence of opportunistic infection at the time on initiation of ART is a clear risk factor for IRIS development. A low baseline CD4 T-cell count, especially below 200 cells/mm³, is also a significant risk factor. Genetic predisposition and certain genes have been associated with increased susceptibility to the development of IRIS. Male gender and younger age have been inconsistently associated with IRIS. Meanwhile type of ART regimen have not been shown to be risk factors for IRIS.

This patient has a low CD4 count (65 cells/mm³). Unfortunately, we had not had time to recheck CD4 at the time when his clinical conditions were rapidly deteriorating. We also didn’t check the viral load yet.

We gave vancomycin and micafungin before ART with tenofovir-lamivudine-efavirenz. We can include this patient to the ART naïve patient because he only took the drug in the first 2 months after being diagnosed with HIV for 3 years.

There is a criteria that establish by Robertson et al. they divided the criteria into two sub. Required criterion: worsening symptoms of inflammation/infection, temporal relationship with starting antiretroviral treatment, symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease, > 1log₁₀ decrease in plasma HIV load. Supportive criterion: increase in CD4 cell count of ≥25 cells/mm³, biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response.

Progressing clinical symptoms in this patient was likely to include the required criterion, so we suggest that IRIS still causes death in this patient after failing to resuscitate attempt. Actually we still guess other causes of the death-like HIV-associated cardiomyopathy that one of the etiology is myocarditis. Various viral and opportunistic infections trigger myocarditis in the setting of uncontrolled HIV infection. Myocarditis is particularly common in late stages of HIV infection. High rates of myocarditis are associated with CD4 counts of less than 400 cells/mm³ and up to two-thirds of untreated AIDS patients having histological evidence of myocarditis on autopsy. However, electrocardiography still on the normal sinus rhythm in this patient.

Morbidity and mortality rates vary according to the pathogen and organs involved, overall mortality in IRIS is reported to be between 0% - 15%, with variability attributed to geography, associated OI, baseline morbidity, and degree of immunosuppression.

### Table 1. CSF examination result

<table>
<thead>
<tr>
<th>Examination</th>
<th>Result</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physics</td>
<td>-0.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muddiness</td>
<td>Clear</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Protein</td>
<td>172.8</td>
<td>mg/dL</td>
<td>15-45</td>
</tr>
<tr>
<td>Glucose</td>
<td>23</td>
<td>mg/dL</td>
<td>-</td>
</tr>
<tr>
<td>Leukocyte Cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMN</td>
<td>2</td>
<td>/mmk</td>
<td>&lt;2</td>
</tr>
<tr>
<td>MN</td>
<td>13</td>
<td>/mmk</td>
<td></td>
</tr>
<tr>
<td>Eritrocyte</td>
<td>1</td>
<td>/mmk</td>
<td>negative</td>
</tr>
</tbody>
</table>

### Table 2. Risk factors for developing IRIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapid decline in viral load (especially in first three months after ART)</td>
</tr>
<tr>
<td>• Low baseline CD4 count (especially &lt;50 cells/mm³ or &lt;10%) and rapid increase after initiation of ART</td>
</tr>
<tr>
<td>• Initiation of ART soon after initiation of treatment for opportunistic infection (OI)</td>
</tr>
<tr>
<td>• Disseminated versus localized OI</td>
</tr>
<tr>
<td>• ART-naïve patient</td>
</tr>
</tbody>
</table>

was undertaken, but attempts were unsuccessful.

**DISCUSSION**

Our patient, 40-year-old man has been diagnosed with HIV withdrawal from drugs with meningoencephalitis. This diagnosis is made based on history, physical examination, and other investigations. Data that supports the history is the presence of fever, accompanied by headache, seizure, and decreased consciousness. There were positive excitability meningeal signs like neck stiffness, Brudzinsky I, and Kernig’s Sign. Physical examination also revealed oral candidiasis. We know from alloamamensa, the patient had HIV since 3 years ago but did not take ART (he only took ART 2 months after the diagnosis).

Meanwhile, MSCT head contrast showed an enhancement in basal cisterna that give us tuberculous meningoencephalitis impression. This is in line with CSF examination from lumbar puncture. The results showed an increase in CSF protein and a decrease in glucose levels, as well as an increase in the number of MN which supported the appearance of TB meningoencephalitis. Regardless of the lumbar puncture results or culture of CSF, patients with symptoms of meningoencephalitis can be started on antibiotics that can cross the blood-brain barrier and steroids.

HIV RNA was detected. In HIV patients, risk of central nervous system infection is related to CD4 levels, where the high risk occurs at CD4 <200 cells/mm³. Clinically in this patient, various opportunistic infections often follow HIV infection such as oral candidiasis and meningoencephalitis so that the patient is included in clinical stage IV based on the severity of HIV-AIDS infection according to WHO provisions. Meanwhile, the very low CD4 results indicate a very severe state of immunodeficiency in the patient.

There are several risk factors for the development of IRIS identified, shown in Table 2. Risk factors for IRIS have been investigated in many studies; however, the cohort differs substantially regarding the study populations and the type of IRIS examined, making conclusions regarding risk factors for IRIS difficult. The presence of opportunistic infection at the time on initiation of ART is a clear risk factor for IRIS development. A low baseline CD4 T-cell count, especially below 50 cells/mm³, is also a significant risk factor. Genetic predisposition and certain genes have been associated with increased susceptibility to the development of IRIS. Male gender and younger age have been inconsistently associated with IRIS. Meanwhile type of ART regimen have not been shown to be risk factors for IRIS.

**CONCLUSION**

IRIS is one of the complications of ART management that increases morbidity and
mortality in HIV patients. This article can be a reference material regarding HIV IRIS. The establishment of diagnostic criteria and clinical pathways needs to be discussed further.

ETHICAL APPROVAL
Patient had received signed written informed consent regarding publication of the medical data in medical journal.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Retnaningsih is the corresponding author and was in charge of reviewing and editing the manuscript. Muchlis Ahsan Udji did the conception of the idea, reviewed and edited the manuscript. Danar performed the literature search, reviewed and edited the manuscript.

ACKNOWLEDGMENTS
This work was supported by Department of Neurology and Internal Medicine, Faculty of Medicine, Universitas Diponegoro.

REFERENCES