

Idiopathic Immunodeficiency in Cytomegalovirus Reactivation: A Rare Case

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Abstract

Idiopathic CD4 lymphocytopenia (ICL) is a rare condition characterized by an unexplained deficit of circulating CD4 T cells leading to increased risk of serious opportunistic infections. Reactivation and severe symptomatic CMV is also a rare case, except in immunocompromised patient. Patient concerns are 36-year-old male patient complained seizure, fever, cough, and dyspnea. History of chronic urticaria and prolonged Meprobamate consumption. HIV was negative. CD4 was low. Diagnosis in this case is Viral encephalitis, Viral pneumonitis, CMV reactivation, hemophagocytic lymphohistiocytosis immunodeficiency state. The results in this study indicate that the patients were treated with conventional therapies for Severe CMV infection with Acyclovir. Steroid was given for the last five days. The first day after administration of therapy showed clinical and laboratory improvement. Laboratory values returned to normal values on the fifth day of therapy. Since the second day after the therapy was given, the patient had no complaints. In cases of CMV reactivation, an immunodeficiency condition should be suspected. A comprehensive history, physical examination, laboratory and radiological examination, adequate therapy and and policy support are required to establish a definite diagnosis and reduce the risk of mortality.

Keywords: Immunodeficiency, CMV reactivation, cytomegalovirus, Idiopathic CD4 lymphocytopenia, CD4.



A. INTRODUCTION

Immunodeficiency is a condition of decreased or lost ability of immune components to fight infection or malignancy. It can be congenital or acquired. Most cases are caused by secondary factors, such as: HIV infection, nutrition, use of immunosuppressants, and malignancy. The primary cause is caused by a genetic defect (McCusker & Warrington, 2011). Components that may be involved: humoral immunity (B cell) deficiency, T cell deficiency, granulocyte deficiency, asplenia, and complement deficiency. Hormonal and metabolic disorders (eg, Anemia, Hypothyroidism, Hyperglycemia), smoking, and a history of alcohol consumption are associated with immunodeficiency status (Gleeson et al., 2004). Idiopathic immunodeficiency is a condition in which the components of the immune system are reduced with unexplained alternative etiologies. Idiopathic CD4 lymphocytopenia (ICL) is a condition defined as persistent CD4 lymphocyte depletion (absolute CD4 count <300 cell/ μ L or <20% of total lymphocytes on two separate occasions 1-3 months apart) in the absence of human immunodeficiency virus (HIV) or any defined immune-deficiency disease or therapy (Ayub et al., 2018).

Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the Herpesviridae family. It infects 60–70% of adults in industrialized nations and >90%

in impoverished countries (Griffiths et al., 2015). CMV infection is typically asymptomatic, but it can be fatal in immunocompromised persons such as HIV-positive individuals, organ transplant recipients, and infants (Munro et al., 2019). There are three types of active CMV infection: initial infection, endogenous infection in CMV-seropositive persons (reactivation), and exogenous infection (different strains) (Varani et al., 2011). In this research, we describe a rare instance of CMV reactivation in a patient with immunodeficiency.

B. METHOD

This research uses qualitative research with descriptive analysis approach. The focus of this research is to analyze Idiopathic immunodeficiency state in cytomegalovirus reactivation. Patient concerns in this study were A 36-year-old male patient complained of seizure, fever, cough, and dyspnea. History of chronic urticaria and prolonged Mebhydrolin consumption. HIV was negative. CD4 was low. The patients were treated with conventional therapies for Severe CMV infection with Acyclovir. Steroids was given for the last five days. Presentation of results and discussion using descriptive method.

C. RESULT AND DISCUSSION

A 36-year-old man was referred to our neurology department in the night shift due to seizures after 1 day of hospitalization in the previous hospital. The patient complained of seizures, twitching of the whole body, one time, the duration of the seizure was about two minutes, and at the time of the seizure the patient was unconscious and the patient's eyes glanced up. One week before, the patient complained of rising and falling fever, the fever did not depend on time, and the fever improved when given fever-reducing drugs. Complaints accompanied by headaches that come and go since 5 days ago. Productive cough with thick white phlegm has been complaining since five days ago.

Complaints accompanied by shortness of breath since two days ago. No sweating at night and weight loss. He has complained of red spots all over his body since a week ago. These complaints often recur since childhood. Patients routinely consume Mebhydrolin Napadisilate every day, for more than five years. A history of hypertension was complained of since 5 years ago, the patient did not take medication regularly and went to the doctor for control. A history of asthma was known since childhood, but after adulthood it never recurred. History of diabetes mellitus, heart failure, tuberculosis infection, COVID-19 was denied. History of taking amoxicillin and paracetamol, one tablet each due to fever. Patients buy their own drugs at pharmacies without consultation and prescription from a doctor.

On physical examination, we found an obese patient with a BMI of 28.3 kg/m². Scattered maculopapular rash, varying in size, itching in the abdominal region, upper, lower, right and left extremities (Figure 2). Physical examination of the head, neck, heart, lungs were within normal limits. Neurological status, meningeal signs, physiological reflexes and pathological reflexes were within normal limits. Laboratory

data is taken directly when the patient arrives at the ER. The first finding at presentation was bicytopenia with leukocytes 3,050/uL and platelets 91,000/uL. The C reactive protein level increased by about 5.4 mg/dL, and the Serum Glutamic Oxaloacetic Transaminase (SGOT) level increased to 68 U/L. Data on renal function, serum electrolytes, hemostasis function, procalcitonin, bilirubin levels, and urinalysis were within normal limits (Table 1). The chest X-ray shows a partially consolidated infiltrate in the lower middle field of the right lung, which leads to pneumonia. CT scan of the head with contrast shows pathological leptomeningeal enhancement in the bilateral parietooccipital region with suspected meningitis, cerebral edema, focal cortical brain atrophy, and pansinusitis (Figure 1).



Figure 1. Radiology findings of the Patient

Figure 1 showing pathological leptomeningeal enhancement in bilateral parietooccipital region suspected meningitis, cerebral edema, focal cortical brain atrophy (A, B). There was a partially consolidated infiltrate in the lower middle field of the right lung (C).

On the second day of treatment, cerebrospinal fluid analysis and culture, blood and sputum cultures, serological markers of infection were taken and examined. The patient was consulted to a pulmonologist for indications of pneumonia, and consulted to the department of internal medicine, infectious tropic division on suspicion of dengue fever. The results of cerebrospinal fluid analysis showed normal results, no inflammatory cells and bacterial morphology were found on Gram stain, acid-fast bacteria were not found on Ziehl Neilsen staining, but did not exclude viral infections. The results of serological examination of infection markers showed positive anti-CMV IgM/IgG and Anti-Rubella IgG (Table 2). The results of the examination showed an increase in ferritin levels by 1957 ng/mL, an increase in triglycerides by 235 mg/dL, and a decrease in CD4 cells to 280 cells/uL (in the condition of leukocytes 5740/uL, and lymphocytes 2810 cells/m³). The patient was diagnosed with viral encephalitis, bicytopenia suspected to be due to hemophagocytic lymphohistiocytosis, viral infection, or agranulocytosis as a result of long-term mebhydrolin napadisylate consumption, pneumonia which may still be viral or bacterial, latent rubella infection, reactivation of cytomegalovirus (CMV) infection, and chronic urticaria. The patient was given IV Levofloxacin 1x750 mg, IV Acyclovir 3x500 mg, IV Hydrocortisone 3x100 mg, and PO Phenytoin 3x100 mg. One day after the therapy, the patient's leukocyte and CRP levels improved, but there was still a decrease in platelets and an increase in

SGOT levels. Two days after administration of therapy, the patient was symptom free. An increase in platelet levels was observed on the second day of therapy. Administration of therapy for five days showed improvement in all laboratory variables. The results of blood and sputum cultures, as well as examination of tuberculosis markers also showed normal results. Due to limited laboratory resources and coinciding with major holidays in Indonesia, RT-PCR examination of CMV DNA can only be examined seven days after being given therapy, with no detectable results of CMV DNA. The patient also planned for a bone marrow examination, then we suggested to consult an ophthalmologist regarding the detection of features of CMV retinitis and a dermatologist regarding chronic urticaria, but the patient refused.



Figure 2. Clinical finding of the Patient

Figure 2, show maculopapular rash on superior, right and left extremities, abdominal region, scattered, variable in size and pruritic

Table 1 Laboratory Data

	Reference Range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 11
Haemoglobin (g/dL)	11.4 - 15.1	13.9	12.9	13.6	14.5	13.9	13.7	13.2	13.4
Leukocyte (/uL)	4.700 – 11.300	5400	3050	2710	5740	12470	11360	9230	9850
Platelet (/uL)	142.000 – 424.000	143.000	91000	64000	23000	34000	70000	213000	474000
ANC (x10 ³ Cell/mm ³)	2.72 - 7.53	4610	2480	2000	2130	3710	4940	5270	7450
TLC (x10 ³ Cell/mm ³)	1.46 - 3.73	470	360	470	2810	6240	4960	2760	3330
CRP	<0,3	5.49			0.63			0.12	
Procalcitonin	<2	0.46			0.23			0.11	
SGOT (U/L)	0-40		68	77	101		121		66
SGPT (U/L)	0-41		31	31	35		89		74
CD4 (Cell/uL)	637 – 1485				280				
Ferritin (ng/mL)	30-400				1957				
Triglyceride (ng/mL)	<150				235				
Urinalysis			Normal						
CSF Analysis			Normal						
CSF Culture			Normal						
Sputum gram culture			Normal flora						
RT-PCR CMV DNA Blood									Not-detected

Note: ANC, absolute neutrophil count; CD4; cluster differentiation 4; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebral spinal fluid; DNA, deoxyribonucleic acid; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TLC, total lymphocyte count

Idiopathic CD4 lymphocytopenia (ICL) is an uncommon illness defined by an unexplained deficiency of circulating CD4 T lymphocytes, which increases the risk of developing severe opportunistic infections. Epidemiology, pathophysiology, etiology, and clinical manifestation are still unknown. There is no known conventional treatment apart from antibiotic prophylaxis (Yarmohammadi & Cunningham et al., 2017). CMV is a herpes virus that often causes asymptomatic latency in the majority of the population. On the basis of serological research, as much as 76% of the general population has a latent infection. By the age of 60, more than 90 percent of the population is seropositive. Reports of reactivation in immunocompetent patients are rare, except in immunocompromised patients. The study reported the prevalence of cases of CMV reactivation in immunocompetent patients was around 18.3%, but in that study the patient population was critically ill and on mechanical ventilation (Tse & Ng, 2014; Zhang et al., 2021). We report a case of CMV reactivation with immunodeficiency state. Even though the lymphocyte count was normal, the patient's CD4 cell count was still low. The patient did not have HIV infection and we found no risk factors for immunodeficiency except a history of chronic urticaria and long-term Mebhydrolin napadisylate consumption.

Table 2. Immunological Profile

Laboratory variables	Value	Reference range
HBsAg	Non-reactive, COI: 0,628	COI <0,9: non-Reactive; COI \geq 0,9 - <1,0: Borderline; COI \geq 1,0: Reactive
Anti-HCV	Non-reactive, COI: 0,066	COI <0,9: non-Reactive; COI \geq 0,9 - <1,0: Borderline; COI \geq 1,0: Reactive
NS1	Non-reactive	Non-reactive
Anti-Dengue IgM	Negative	Negative
Anti-Dengue IgG	Negative	Negative
Anti-HIV	Non-reactive	Non-reactive
Anti-CMV IgM	1,72	Negative < 0,7 COI; Indeterminate \geq 0,7 - <1,0 COI; Positive \geq 1,0 COI
Anti-CMV IgG	45,98	Negative < 0,5 U/mL; Indeterminate 0,5 - <1,0 U/mL; Positive \geq 1,0 U/mL
Antigen SARS-CoV-2	Negative	Negative
Anti-HSV-1 IgM	8,0	Negative < 20 U/mL; Borderline 20-25 U/mL; Positive > 25 U/mL
Anti-HSV-1 IgG	2,2	Negative < 20 U/mL; Borderline 20-25 U/mL; Positive > 25 U/mL
Anti-HSV-2 IgM	6,2	Negative < 20 U/mL; Borderline 20-25 U/mL; Positive > 25 U/mL
Anti-HSV-2 IgG	2,6	Negative < 20 U/mL; Borderline 20-25 U/mL; Positive > 25 U/mL
Anti-Rubella IgM	0,45	Negative < 0,8 COI; Indeterminate \geq 0,8 - <1,0 COI; Positive \geq 1,0 COI
Anti-Rubella IgG	41,86	Negative < 10 U/mL; Positive \geq 10 U/mL
VDRL	Non-reactive	Non-reactive
TPHA	Non-reactive	Non-reactive
RT-PCR SARS-CoV-2	Negative	Negative

Note: CMV, cytomegalovirus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; NS1, nonstructural protein 1; RT-PCR, Real time polymerase chain reaction; COI, cutoff index; TPHA, Treponema Pallidum Hemagglutination Assay; VDRL, Venereal Disease Research Laboratory

Several immunosuppressive drugs such as steroids, cytotoxic chemotherapy and autoimmune disorders have been reported as risk factors for CMV reactivation (Furuta et al., 2020). Mebhydrolin napadisylate is an antihistamine that has been reported to have adverse effects on agranulocytosis and neutropenia (Limaye et al., 2008). In our reports, Mebhydrolin napadisylate was the only suspected drug. The patient took the drug for a long term (more than five years), without a doctor's

recommendation and prescription, because the patient had a history of chronic urticaria. Initiation of viral replication from latency is not only driven by immunosuppression, but also appears to be associated with immunological activation, similar to HIV (Decrion et al., 2005). For instance, tumor necrosis factor (TNF)- α , which is generated during inflammation, can reactivate the virus. On latently infected cells, TNF- interacts to the TNF receptor, providing signals that activate nuclear factor-kB. (NF-kB). Thus, the activated p65/p50 NF-kB heterodimer translocates into the nucleus and attaches to the IE enhancer region of CMV, initiating viral replication (Docke et al., 1994). This molecular mechanism has a clinical connection in which the reactivation of latent CMV is related with higher serum levels of TNF- α in atopic dermatitis and sepsis patients (Varani & Landini, 2011; Da Cunha & Wu, 2021).

In immunocompetent people, CMV often causes an asymptomatic or minimally symptomatic acute infection. In immunocompromised hosts, however, CMV infection can cause a wide range of clinical manifestations, such as mononucleosis syndrome, hemolytic anemia, thrombocytopenia, liver function abnormalities, retinitis, pneumonitis, encephalitis, hepatitis, esophagitis, and colitis (Limaye et al., 2008). If left untreated, CMV reactivation can lead to serious complications within a few weeks (Yarmohammadi & Cunningham et al., 2017). Since the signs and symptoms of CMV disease often overlap with other infectious processes and rejection, the diagnosis is made by integrating the clinical history, clinical presentation, and laboratory data (Furuta et al., 2020). Encephalitis and pneumonitis accompanied by pancytopenia were the presenting manifestations in our case report.

Appropriate diagnostic tests are essential for the management of CMV infection and disease in immunocompromised patients. Several diagnostic modalities are available, including serology, quantitative polymerase chain reaction (PCR), pp65 antigenemia, culture, and histopathology (Ross et al., 2011). The gold standard for CMV infection is positive findings on PCR and viral culture of CMV. Determination of the sample to be taken is primarily based on the anatomic site, where CMV manifestations are suspected (Bonalumni et al., 2011). However, the detection of CMV virus DNA through laboratory examination is difficult, where each method of examination and the type of sample used has low sensitivity and specificity. In this case, our CMV DNA PCR detection was only able to be checked 7 days after therapy. This was due to the unavailability of examinations at our hospital which required sending samples to laboratories outside the province.

Intravenous ganciclovir is the medicine of choice for the treatment of CMV illness, however valganciclovir may be used for non-severe CMV infections (Ross et al., 2011). Although acyclovir is not as effective as ganciclovir, research indicates that it delays 32% of CMV infections and prevents 59% of CMV illness cases in the placebo cohort (Ross et al., 2011). European transplant groups are more likely than their American counterparts to utilize acyclovir or valacyclovir for CMV prophylaxis (Reicsching et al., 2015). After the diagnosis of viral encephalitis and pneumonitis suspected to be caused by reactivation of CMV in idiopathic immunodeficiency cases,

we immediately started acyclovir therapy. Our national formulary policy limits the use of ganciclovir and valganciclovir to patients with CD4 cells below 100 cells/L and evidence of organic disorders (such as CMV retinitis and encephalitis) or in cases of organ transplantation from CMV-infected donors. Steroid therapy in patients based on the possibility of suspicion of hemophagocytic lymphohistiocytosis syndrome (In our patient we found fever, bicytopenia, increased ferritin levels, triglycerides, SGOT, and decreased fibrinogen levels), unfortunately the patient refused to consult our ophthalmologist for evaluation regarding the possibility of CMV retinitis, and refused bone marrow aspiration.

D. CONCLUSION

Idiopathic CD4 lymphocytopenia is a condition characterized by low CD4 counts. It is rare and most of the information about this illness comes from case reports. CMV reactivation are very rare in an immunocompetent host. CMV reactivation varies from asymptomatic to severe syndromes and if left untreated, CMV reactivation can lead to serious complications, especially in immunocompromised patient.

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