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Case Report

Methisoprinol as an immunomodulator for treating infectious mononucleosis

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ABSTRACT

Background: *Infectious mononucleosis (IM) is the self limiting disease that associated with primary Epstein Barr virus (EBV). It is a gamma herpes virus. EBV infection is follows saliva-transfer by kissing or sexual intercourse. The most clinical manifestation in IM consists mainly of the specific sign: pharyngitis, fever, and lymphadenopathy. The main therapy is supportive treatment. Actually the antiviral therapy is required for the host with high response immune.* ***Purpose:*** *The aimed of this study was to report the therapy of IM using methisoprinol.* ***Case:*** *The woman patient, 33 years old, came to hospital by suffering pharyngitis and swolen on left neck. It had been since 3 days ago.* ***Case management:*** *She had come to Puskesmas that were given amoxycillin capsul 500 mg three times a day for three days and paracetamol tablet 500mg three times a day for three days, but she was still ill. Then she came to RSGM Hasan Aman Banjarmasin. She was diagnosed as IM. The instruction were isolation and bed rest for a week. She had to eat sofly and drink water highly. The therapy were amoxycillin capsul 500 mg three times a day for seven days, methisoprinol caplet 500 mg three times a day for seven days, natrium dikofenak tablet 50 mg three times a day for seven days. She was asked to see the dentist next 7 days. In this case, she were not given acyclovir.* ***Conclusion:*** *IM is self limiting disease. IM is the disease with spesific clinical syndrome that associated with primary EBV infection. Depend on the base of clinical experiences, the supportive treatment is adviced for patient of IM. Methisoprinol has both immunomodulator and antiviral properties.*

Keywords: *Epstein Barr Virus; immunomodulator; infectious mononucleosis; methisoprinol*

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INTRODUCTION

Infectious mononucleosis (IM) is a disease with clinical syndrom associated with primary Epstein–Barr virus (EBV) infection. EBV is a gamma herpes virus that has the double stranded DNA genome of about 172 kb. EBV infection occurs in humans that make the results in a life long infection. IM is one of an acute self limiting disease.[1]

Approximately 90% of EBV infects adults permanently. EBV often be transmitted subclinically between the children through saliva. In adolescents, it is clinical manifestation of IM that are pharyngitis, cervical lymphadenopathy, fever, and malaise.[2] EBV infection through transfering saliva by kissing or sexual intercourse.[2-4] Infants and children show an asymptomatic or mild manifestation of EBV infection. It is different from adolescents with the age of 15–25 years that have the highest incidence of IM in the United States, Japan, United Kingdom, and Europe.[5] Each year, approximately 10 to 20% of people become infected. IM is happened in 30 to 50% of these patients. There are no obvious annual cycles and no specific season in incidence. There is no affected by the basis of sex.[1]

The most clinical manifestation in IM shows the specific signs: fever, pharyngitis, and lymphadenopathy. The laboratory results of IM patients show the lymphocytosis with atypical lymphocytes.[6] IM by EBV infection show approximately 0.5% of the total lymphocyte population that is infected. Fever, cervical lymphadenopathy, sore throat, sometime show the dusky soft exudate around the tonsillar rings, pain, tender left upper quadrant splenomegaly, and atypical lymphocytosis distinguish glandular fever. EBV replicates T and B lymphocyt cells in salivary gland.

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During the viremia of explosive primary infection, liver, thyroid, brain, meninges, myocardium, and pericardium may be affected. EBV may be also transferred by blood transfusion.[5]

Primary infections in young children are sometime showed as non specific disease, because the typical signs of IM are unclear. IM sometime affects people that have primary EBV infection during or after the second decade of life. Economic and sanitary conditions have improved over past decades, EBV infection in early childhood has become less common, and more children are risk suspectable as they are adolescence.[1] The incubation period between exposure and manifestation of the symptoms can happen in 30 to 60 days, so that make the identification of the initial exposure is difficult.[4] This study reports the therapy of IM using methisoprinol as different therapy besides acyclovir. Methisoprinol has both immunomodulator and antiviral properties.

CASE

The woman, 33 years old came by suffering pharyngitis and the swolen under her left ear. She had been febris for three days and suffering pharyngitis. After three days, there was the swolen and painful under her left ear. She was going to Puskesmas that given amoxycillin capsul 500 mg three times a day for three days and paracetamol tablet 500 mg three times for three days.

CASE MANAGEMENT

1st Visit (4 days): the drugs from Puskesmas was finished. She was still subfebris. There were the swolen and painful under her left ear bigger than before. She got disphagia, so she did not eat. The extraoral examination was showed the swolen under her left ear, normal color, pain, hard, unmovable and diffuse border on her left neck (Figure 1). The intraoral examination showed the swolen, red and painful on her left oropharyng (Figure 2).

The patient was diagnosed as IM. It based on mainly manifestation of the specific signs such as pharyngitis, fever, and lymphadenopathy. The instruction were isolation and bed rest for a week. She had to eat the smooth meals and much water. The therapy were given amoxycillin capsul 500 mg three times a days for seven days, methisoprinol caplet 500 mg three times a day for seven days, natrium diklofenac tablet 50 mg three times a day for seven days. She was asked to see the dentist next 7 days.

2nd Visit (11 days): the patient was cured. The drugs was finished. She regularly took the prescribed medicine. The swolen under left ear was gone. The pharyng was not painful, so she could eat again. The extraoral examination of her neck showed the normal condition (Figure 3) and so did the intraoral examination (Figure 4). She could swollen well without pain, so that could eat again.

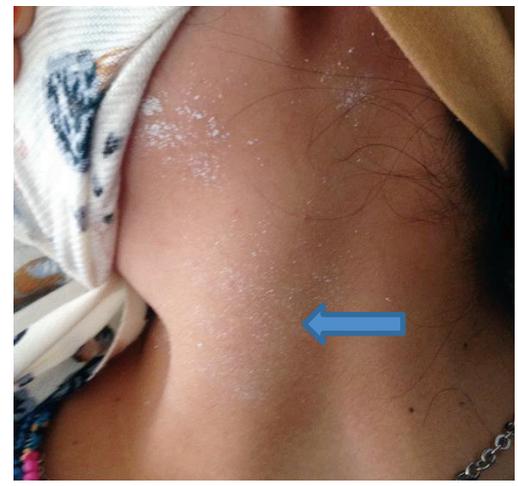

Figure 1. The extraoral examination showed swolen, painful, normal color, unmovable, and diffuse border on her left neck.

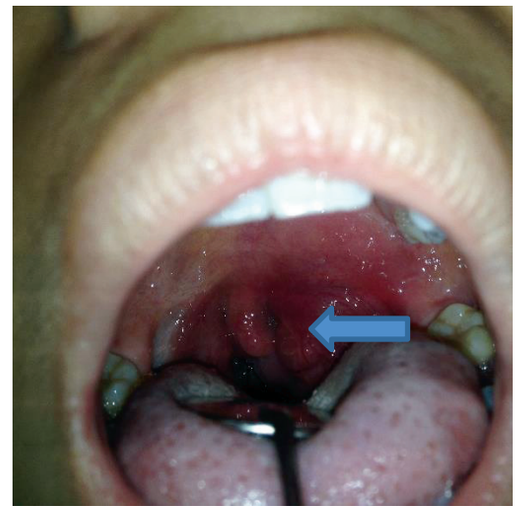

Figure 2. The intraoral examination showed swolen, painful, red, and clear border on her left oropharyng.

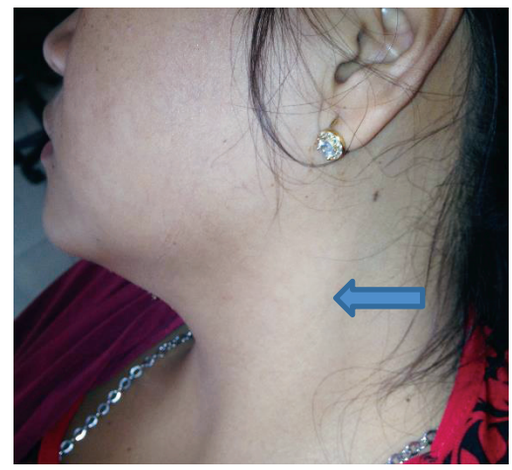

Figure 3. The normal condition without swolen and pain was on her left neck.

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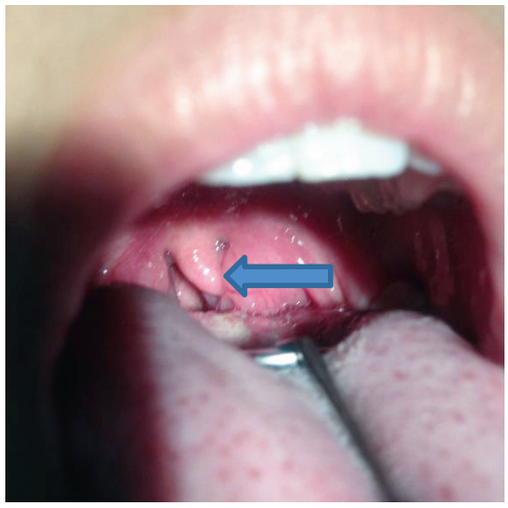

Figure 4. The normal condition without swolen and pain was on her left oropharyng.

DISCUSSION

Differential diagnosis of IM are pharyngitis by group A *Streptococcus*. It has the same of IM symptoms such as sore throat and fever. It can be definited by the bacterial culture examination. Diagnostic testing of IM are determined by EBV antibody serologies as Ig M , Ig G, and EBV nuclear antigen antibody (EBNA). Unfortunately, the EBV antibody peak with in two to six weaks after the onset of the symptoms.[4] It is important to treat patient of IM based on the specific clinical examination as malaise, fever, sore throath, exudate upon the tonsillar rings, and lymphadenopathy. By anamnesis and clinical manifestation, the final diagnosis can be determined immediately then the patient can be treat.

The lymphocytes in IM are promoted by the composed of the mixture of CD8+ cytotoxic suppressor T cells, NK cells, and CD4+ helper T-cells. The most population is the CD8+ T cells, which have a role in the suppression of viral replication and have cytotoxic activity against the virus that infect B cells. Increased numbers of CD8+ cytotoxic suppressor T cells also have been showed in other virus infections, including HIV, cytomegalovirus, and hepatitis C infections. The virus penetrates through the oropharyngeal epithelium. It replicates in the oropharyngeal epithelium cells especially B-lymphocytes. EBV binds to B-lymphocytes, through CD21 their antigen promotes their transformation and proliferation. In the course of infection, the blood examination shows the large number of atypical lymphocytes resulting from the polyclonal activation of cytotoxic suppressor CD8 cells. They limit the excessive transformation and proliferation of B cells. In the event of inefficacious T cell immune response, it can develop persistent infection and uncontrolled B cell proliferation that is in the basis of the EBV oncogenic potential.[7] The unlimit stimulation of EBV to B cells and the general condition under the low immune response make the cells proliferation for being neoplastic B cells. It will stimulate the Burkitt's lymphoma.[7,8]

Base on the clinical examination, supportive care is recommended for patients with IM. Acetaminophen or non steroidal anti inflammatory drugs are recommended to manage fever, sore throat, and malaise. Adequate fluid and nutrition intake should be given. The adequate rest is required. Using acyclovir did not significantly reduce the peripheral blood of EBV levels or the duration and severity of clinical symptoms.[9] Some control trials on treatment with acyclovir in patients with EBV have shown that treatment never decrease the severity of clinical signs nor their duration.[10] In cases, the diagnosis of IM is unclear. EBV specific serologic testing may be used to definitively diagnose primary EBV infection. The main therapy is supportive treatment. Actually the antiviral therapy is required for the host with high response immune. Corticosteroid drugs are not indicated.[9] The majority of patients with IM recover without sequelae and return to normal activities within 2 months after the onset of symptoms. IM is the self limiting disease, so that was depend on the host immune response.[1,8]

Acyclovir did not use to treat it, because this drug only prevents virus replication. Acyclovir works through three mechanisms.The first is the phosphorylation of the drug within the cell to the phosphate derivative by viral thymidine kinase. Since acyclovir is a poor substrate for healthy cell's thymidine kinases this step happens much more rapidly in infected cells. Further metabolism via a cellular enzyme that is present in all cells called guanosine monophosphate kinaseresults in di-and tri-phosphate derivatives. The second mechanism of action for acyclovir is the inhibition of DNA polymerase by the active acyclovir. Since acyclovir triphosphate is an acyclic nucleoside analog that competes with dGTP it becomes incorporated into the viral DNA chain during synthesis in the nucleus. The inhibition of DNA polymerase is due to the fact that the drug lacks essential groups that the normal building blocksof the viral DNA have. Cyclic sugars are missing in acyclovir triphosphate and cause chain elongation termination.[11]

This case report that the patient was given methisoprinol 500 mg three times a day for seven days. Methisoprinol has both immunomodulator and antiviral properties. Methisoprinol is a well known immunostimulator that has been used for years. The active agents of isoprinosine are the compound of inosine and 1-(dimethylamino/2-propanol/4-acetamidobenzene at a ratio of 1:3). It has a stimulatory effect on cellular and humoral defense mechanisms in both humans and animals. It activates T and B lymphocytes increasing the capacity of their proliferative response to antigens and mitogens, particularly in individuals with lowered resistance. Methisoprinol also increases the proliferation of macrophages and their phagocyte activity. Additionally, it induces the excretion of interferon and corrects the ability of cells under the influence of immunosuppresants to synthesize it.[12] Methisoprinol is the value treatment of acute and chronic viral infections,

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and also as a prophylactic. It works on the immune system to repair the impaired mediated cell immune response for getting normal cells.[13]

Methisoprinol also has the direct antiviral activity. It will decrease the intensity of symptoms and stop the duration of a viral infection. In addition, the incidence of complications is reduced. It is the frequency and severity of IM recurrences. The drug can be prescribed during the disease as a prophylaxis against reactivation of latent viral infections such as herpes simplex or varicella zooster. It is also used for the treatment or management of other secondary viral infections. Methisoprinol is the drug with a synthetic purine derivative of immunomodulatory and antiviral properties, which result from an unconnected in vivo increasing of host immune responses.[13]

The action of methisoprinol can be normalizes the cell mediated immunity by promoting the differentiation of T lymphocytes into T cytotoxic cells and T helper cells, and increasing lymphokine production, production of IL-1, IL-2 and IFN-gamma, and NK cell functions. It is also enhancing the humoral immune response by promoting the differentiation of B lymphocytes into plasma cells and increasing the antibody production, the number of IgG and complement surface markers, neutrophil cells, monocyte cells, macrophage chemotaxis and phagocytosis. It can inhibit the viral growth by suppressing the viral RNA synthesis while potentiating depressed lymphocytic working.[12,13]

In conclusion IM is self limiting disease. IM is a specific signs that is sometime associated with primary EBV infection. Base on the clinical examination, the supportive treatment ahall be given to IM patients. The therapy by using acyclovir did not significantly reduce the severity of clinical symptoms. This case used methisoprinol that has both immunomodulator and antiviral properties.

REFERENCES

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med 2010; 362(21): 1993-2000.
2. Balfour HH Jr, Dunmire SK, Hogquist KA. Infectious mononucleosis. Clin Transl Immunology 2015; 4(2): e33.
3. Macsween KF, Higgins CD, McAulay KA, Williams H, Harrison N, Swerdlow AJ, Crawford DH. Infectious mononucleosis in university students in the United kingdom: evaluation of the clinical features and consequences of the disease. Clin Infect Dis 2010; 50(5): 699-706.
4. Rogers ME. Acute infectious mononucleosis: a review for urgent care physicians. American Journal of Clinical Medicine 2012; 9(2): 88-91.
5. Lerner AM, Beqaj SH, Gill K, Edington J, Fitzgerald JT, Deeter RG. An update on the management of glandular fever (infectious mononucleosis) and its sequelae caused by epstein barr virus (HHV-4): new and emerging treatment strategies. Virus Adaptation and Treatment 2010; 2: 136-45.
6. Kunimatsu J, Watanabe R, Yoshizawa A. Eipstein-barr virus infectious mononucleosis in a splenectomized patient. J Med Cases 2013; 4(6): 353-6.
7. Karcheva M, Lukanov T, Gecheva S, Slavcheva V, Veleva G, Nachev R. Infectious mononucleosis – diagnostic potentials. Journal of IMAB - Annual Proceeding 2008; 14(1): 9-13.
8. Apriasari ML, Baharuddin EM. Penyakit infeksi rongga mulut. Surakarta: Yuma Pustaka; 2012. p. 15-6.
9. Apriasari ML. Kumpulan kasus penyakit mulut. Jakarta: Salemba Medika; 2013. p. 19-20.
10. Busch D, Hilswicht S, Schöb DS, Trotha KT, Junge K, Gassler N, Truong S, Neumann UP, Binnebösel M. Fulminant eipstein-barr virus - infection mononucleosis in an adult with liver failure, splenic rupture, and spotaneous esophageal bleeding with ensuing esophageal necrosis: a case report. J Med Case Rep 2014; 8: 35.
11. Lemke TL, Williams DA, Roche VF, Zito W. Foye's principles of medicinal chemistry. 6th ed. Baltimore: Wolters Kluwer Health/ Lipincott Williams & Wilkins; 2008. p. 122-5.
12. Kazun B, Siwicki AK. Impact with Bioimmune with methisoprinol on non-specific cellular and humoral defense mechanisms and resistance of African catfish (Clarias gariepinus) to experimental infection with iridovirus. Arch Pol Fish 2013; 21: 301-14.
13. Sardana V, Sharma D, Agrawal S. Subacute sclerosing panencephalitis revisited. International Journal of Basic and Applied Medical Sciences 2013; 3(1): 225-41.

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