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Case Report

Dapsone hypersensitivity syndrome: a case in rural area of Indonesia

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ABSTRACT

Dapsone hypersensitivity syndrome is a potentially fatal adverse drug reaction ranging from mild to severe involvement. If left unrecognized and untreated, this syndrome may lead to death. We reported a 19-year-old female with dapsone hypersensitivity syndrome in the rural area of Papua, Indonesia. The diagnosis was made clinically with some supporting laboratory examinations. The patient was planned to be given systemic corticosteroid of dexamethasone along with supportive care. However, due to the limited resources, dexamethasone could not be given daily to the patient leading to a poor clinical outcome.

Keywords: Dapsone, Dapsone hypersensitivity syndrome, Morbus Hansen

INTRODUCTION

Dapsone is an antibiotic and anti-inflammatory agent of the sulphone group. Dapsone can be used alone or in combination with other medications to prevent and treat several infectious diseases, including Morbus Hansen. Dapsone hypersensitivity syndrome is currently estimated to be found in 3.6% patients consuming dapsone. The incidence of this syndrome increases in parallel to the increased dapsone prescription for Morbus Hansen and as a chemophrophylaxis for *P. jirovecii* on patients with human immunodeficiency virus (HIV) infection. This syndrome is also more commonly found in patients receiving a multi-drug therapy (MDT).[1-3]

This syndrome is caused by adverse reaction of the medications characterized by the clinical triad of fever, itch, and systemic involvement (usually the hepatobiliary and hematological system), which can lead to organ system dysfunction and ultimately death. Up to this date, there are no supporting examinations to predict the risk of dapsone hypersensitivity syndrome. Main treatment of this symptom is the cessation of the causative drug, systemic corticosteroid administration, identification of organ systems involved, skin treatment, and supportive care.[4,5] Although dapsone is considered one of the most important drug to treat Morbus Hansen, careful considerations regarding adverse reactions, including scheduling, drug rationale, and holistic care are needed to treat patients with this syndrome.[3]

We reported a case of 19-year-old female with dapsone hypersensitivity syndrome, diagnosed in a resource-limited setting, with no availability of dermatologist and systemic corticosteroid in which the patient was hospitalized.

CASE REPORT

A 19-year-old female was referred from Paniai District General Hospital (RSUD Paniai) to Nabire District General Hospital (BLUD RSUD Nabire) on 12 August 2022, with the diagnosis of Morbus Hansen with a differential diagnosis of Stevens-Johnson syndrome. The patient had chief complaint of exfoliating skin on all over her body for 3 weeks prior to hospitalization. The lesions initially started around the hands, then spread to the entire body. The patient also complains of itchy skin, yellow-colored eye and nails, painful lesions on eye and mouth

mucosa, swelling on face and hand, lumps on the neck, upper right abdominal pain, nausea, and vomiting.

Figure 1: Clinical characteristics of the patient.

The patient was previously diagnosed with Morbus Hansen and was treated with MDT-PB consisting of rifampicin and dapsone from a primary health care center 2 months prior to examination. Symptoms of exfoliating skin, fever, and icterus after consuming MDT for 6 weeks. The patient continued to take the MDT for 6 weeks after the symptoms showed up. The patient did not seek for any healthcare due to a long distance of the health centers to her house. The patient presented to RSUD Panian 3 weeks after the symptoms erupted due to lethargy and low food intake due to mouth ulcers and stomach pain. The patient had never had the same symptoms before. History of treatment with anti-tuberculosis and anti-retroviral medications were denied.

On physical examination, blood pressure was 100/80 mmHg, pulse rate 98 beats per minute, respiratory rate 20 times per minute, axillary temperature 37.0ºC, oxygen saturation 95% on room temperature. Anemic conjunctiva, icteric sclera, and bilateral multiple lymphadenopathies were found. Vesicular lung sounds were found, with no rhonchi and wheezing. No murmurs were found. Bowel sounds were normal, percussion was tympanic, accompanied with epigastric palpation pain, hepatomegaly 2 fingers below costal arch, with no splenomegaly. Extremities were warm, pitting edema were found on dorsal part of hand, along with icteric nails. Dermatologic status, location of entire body, multiple hyperpigmented patch-plaque, size 0.5×1 cm-5×10 cm, well-defined border, geographical-shaped, generalized-spread, accompanied with scales, hemorrhagic crusts, ulcers, and fissures.

Supporting examinations at RSUD Panian on 11 August 2022, showed WBC 11.98×103 /ul, RBC 1.21×106 /ul Hb 3.7 gr/dl, HCT 11.8%, MCV 97.7, MCH 30.6, PLT 149×103/ul, AST 63.3 U/l, ALT out of control, creatinine 0.39 mg/dl, random blood sugar 98 mg/dl. Immunoserology tests of HbsAg, Anti-HbsAg, and anti-HIV were all non-reactive. Supporting examinations at BLUD RSUD Nabire on 12 August 2022, showed WBC 6.80×103 /ul, RBC 0.80×106 /ul, Hb 2.8 gr/dl, HCT 9.1%, MCV 113.8, MCH 35.0, PLT 88×103 /ul, AST 81.0 U/l, ALT 33.0 U/l, creatinine 0.38 mg/dl, albumin 2.1 g/dl, random blood glucose 156 mg/dl. Blood smear showed macrocytic anemia, suspected megaloblastic anemia with transient thrombocytopenia. A working diagnosis of dapsone hypersensitivity syndrome was made.

The patient was given IVFD NaCl 0.9% 1 liter loading with 20 drops per minute as maintenance, ceftriaxone 2 grams every 24 hours intravenously, vitamin C 1 gram every 12 hours intravenously, curcuma tablet every 8 hours orally, ferrous sulphate 320 mg every 24 hours orally at RSUD Paniai on 11 August 2022. When referred to emergency room of BLUD RSUD Nabire, the patient was given oxygenation with nasal cannula 3 liters per minute, IVFD NaCl 0.9% 20 drops per minute, ceftriaxone 2 grams every 24 hours intravenously, ranitidine 30 mg every 12 hours intravenously, paracetamol 1 gram every 12 hours intravenously, curcuma tablet every 8 hours orally. Due to the unavailability of a dermatovenereologist in BLUD RSUD Nabire, the patient was consulted to department of internal medicine, and was given vitamin B complex 2 tablets every 8 hours orally, acetylcysteine 250 mg/ml 25 ml drip every 12 hours intravenously, dexamethasone 5 mg every 8 hours intravenously, and 4 bags of packed red cells transfusion. In addition, the patient was prescribed betamethasone valerate 0.1% cream every 8 hours topically on skin lesions. Dexamethasone could not be given daily due to the unavailability of the stocks in the hospital.

Follow-up examination on 22 August 2022, the patient still complaints of the same exact symptoms without any changes. On physical examination, blood pressure was 100/60 mmHg, pulse rate 116 beats per minute, respiratory rate 22 times per minute, axillary temperature 37.2ºC, oxygen saturation 94% on room air. Anemic conjunctiva, icteric sclera, and bilateral multiple lymphadenopathies were found. Vesicular lung sounds were found, with no rhonchi and wheezing. No murmurs were found. Bowel sounds were normal, percussion was tympanic, accompanied with epigastric palpation pain, hepatomegaly 2 fingers below costal arch, with no splenomegaly. Extremities were warm, pitting edema were found on dorsal part of hand, along with icteric nails. Dermatologic status, location of entire body, multiple hyperpigmented patch-plaque, size 11 cm-5×10 cm, well-defined border, geographical-shaped, generalized-spread, accompanied with scales, hemorrhagic crusts, ulcers, and fissures. Diagnosis of follow-up dapsone hypersensitivity syndrome was made. The patient was given curcuma tablet every 8 hours orally, Hepagard® supplement 2 tablets every 8 hours orally, cefadroxil 500 mg every 12 hours orally,

paracetamol 500 mg every 8 hours orally, ranitidine 150 mg every 12 hours orally, ferrous sulphate 320 mg 2 tablets every 6 hours orally, and betamethasone valerate 0.1% cream every 8 hours topically on skin lesions.

DISCUSSION

Dapsone (4, 4'-diaminodifenilsulfon) is a medication clinically used for more than 60 years. Dapsone can treat and prevent infectious diseases such as Morbus Hansen, *Pneumocystis jirovecii*, toxoplasmosis, and malaria. In addition, dapsone can be used for several dermatological conditions, including bullous dermatitis, acne vulgaris, cutaneous vasculitis, and herpetiform dermatitis. Side effects of dapsone range from mild to severe forms, including gastric irritation, headaches, insomnia, blurry vision, paresthesia, fever, hematuria, itch, methemoglobinemia, hemolisis, hepatitis, and dapsone hypersensitivity syndrome.[4,6]

A generalized adverse effect of dapsone is defined as dapsone hypersensitivity syndrome. This syndrome usually happens 3-5 weeks after dapsone initiation. This syndrome is characterized with a clinical triad of fever, itch, and systemic involvement (usually hepatobiliary and hematological systems), which can lead to organ system dysfunction and ultimately death.[7] Incidence of this syndrome was estimated to be 3.6% of all patients consuming dapsone, which had seen a constant increase in the past few decades. This syndrome had a high mortality rate up to 9.9%.[8] Although the exact pathophysiology of this syndrome remained unclear, currently there were three main hypotheses believed to have caused this syndrome, including humoral immune response, delayed hypersensitivity reaction, and liver metabolism disorders causing acetylation, hydroxylation, and toxic metabolic products.[9]

Clinical manifestation of dapsone hypersensitivity syndrome include the triad and can be accompanied by lymphadenopathy, eosinophilia, hepatitis, acute pneumonitis, and other multi organ dysfunctions. The patient on this case complained of exfoliating skin, itch, fever, and icteric. Diagnostic criteria were applied clinically using Richardus and Smith criteria: (1) symptoms arose within 8 weeks of dapsone initiation and recovers after dapsone cessation; (2) symptoms were not caused by other medications given in combination with dapsone; (3) symptoms were not caused by leprosy reaction; (4) symptoms were not caused by other conditions; (5) two of the following symptoms were found, including fever, skin eruption, lymphadenopathy, hepatomegaly, jaundice, and abnormal liver function tests.[6]

Dapsone hypersensitivity syndrome is managed by dapsone cessation, systemic corticosteroids, identification of involved organ system, skin, and supportive managements. Follow-up examinations were necessary to weigh risks of recurrencies due to deposits of toxic metabolites on skin, muscle, liver, or kidneys. Screening for hepatitis B and HIV need to be done to determine mortality risk of the patient.[4] The patient on this case had been given all medications mentioned above. However, due to limited resources, corticosteroid injection of dexamethasone was not given daily due to the unavailability of the medication in the hospital. This caused delayed clinical improvement, until the patient and her family asked to return home on their behalf. In addition, there were no dermatovenereologists in the hospital where the patient was hospitalized. Therefore, general practitioners should be able to know signs and symptoms of dapsone hypersensitivity syndrome, in order to give prompt treatment to the patient, especially those practicing in very limited resource setting.

CONCLUSION

Dapsone can be used for immunological, inflammatory, and dermatological conditions. Due to the increase of dapsone use especially for Morbus Hansen, dapsone hypersensitivity syndrome were also seen to be increasing. Healthcare workers in high dapsone use are recommended to know signs and symptoms of this syndrome in order to give prompt treatment for patients with this syndrome, to prevent the risk of morbidity and mortality this syndrome poses.

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