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Pancytopenia and Progressive Splenomegaly in Patient with Disseminated Histoplasmosis

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ABSTRACT

Disseminated histoplasmosis is a severe manifestation of fungal infection caused by *Histoplasma capsulatum*. It usually occurs in a patient with an immunodeficiency state. With the increase of HIV infection and the use of immunosuppressant drugs lately, its prevalence also increases. A case of 43 years old female with prolonged fever, pancytopenia, and massive progressive splenomegaly. The diagnosis of disseminated histoplasmosis and the secondary hemophagocytic syndrome was made based on bone marrow examination that showed increased hemophagocytic processes and multiple intracytoplasmic *H.capsulatum.* She had been treated with Itraconazole 200 mg for three months. In the first month's evaluation, her complete blood count improved without any transfusions, and the size of her spleen size decreased. She had been fully recovered after the completion of 3-month treatment.

Keywords: Disseminated histoplasmosis, immunodeficiency, hemophagocytic syndrome, pancytopenia, splenomegaly

In 1906, Darling, an American Pathologist, introduced a fatal disseminated histoplasmosis case. Many decades later, it was reported that histoplasmosis was caused by a dimorphic fungus called *Histoplasma capsulatum.* Approximately 40 million people in United States have been infected with *H.capsulatum*, and 60-90% of people living in Ohio and area near the Mississippi River are exposed to this fungus. The soil containing bird's and bat's dropping is the best medium for the growth of *Histoplasma capsulatum. Histoplasma* spores spread through the inhalation of these spores in people in an endemic area. The histoplasmosis manifestation becomes severe in the case of immunocompromised patients. It is reported that 40 million people have been infected with *H.capsulatum*, and there are 500.000 new cases every year in the United States. It is reported that the prevalence of histoplasmosis in Indonesia is 13.6% in the population of a young adults. As the increase of HIV infection in the last few decades, the opportunistic infection caused by *H.capsulatum* also increases.[1] The proportion of histoplasmosis as the opportunistic infection is 2% among AIDS patients in Indonesia.[2] This report presents a case with the clinical manifestation, diagnosis, and therapy of disseminated histoplasmosis in immunocompromised adults.[2,3]

CASE

A female, 43 years old, had been hospitalized in a private hospital in Surabaya in the middle of July 2017 with the complaint of prolonged fever, body weakness for four weeks, and subconjunctival bleeding for a week. There was a progressive abdominal enlargement in the last month. In physical examination at the admission time, the patient was anemic, and she had a fever with 38.5^{0}C body temperature and massive splenomegaly (schuffner 4). The patient had no medical history with the same disease and medication before. She lived in an urban area and worked as a lawyer. There was no history of animal contact before. Her hemoglobin level was 8.9 g/dL with normochromic normocytic erythrocyte morphology, leukocyte count was 1,800/µL with the majority of segmented neutrophils, and platelet count was 33,000/µL. The reticulocyte count was 0.4%. The total protein was 6.3 g/dL, albumin was 3.1 g/dL, serum aspartate aminotransferase was 45 U/L, serum alanine transaminase was 65 U/L, blood urea nitrogen was 8 mg/dL, serum creatinine was 0.6 mg/dL. Her serology results were negative for HbsAg, anti HCV, and HIV serology (antibodies to HIV-1, HIV-2, and HIV-1 p24 antigen); however, her CD4$^+$ lymphocytes decreased to 143 cell/µL. The patient was diagnosed with pancytopenia with splenomegaly.

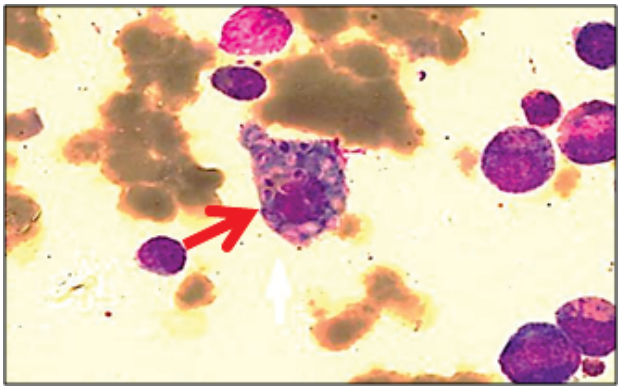

Figure 1. Bone marrow aspirate examination. There are multiple intracytoplasmic *Histoplasma capsulatum* with the clear perinuclear zone (red arrow)

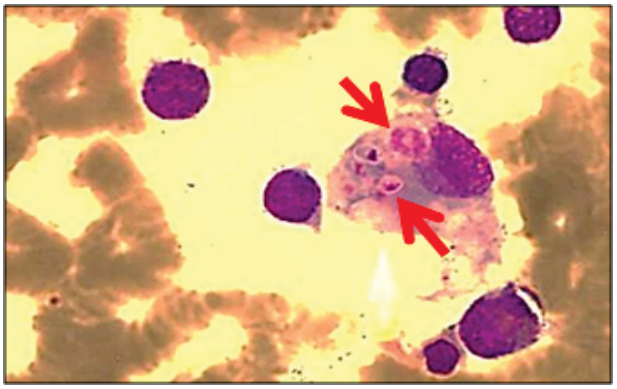

Figure 3. Bone marrow aspirate examination. The hemophagocytic process and *H.capsulatum* inside

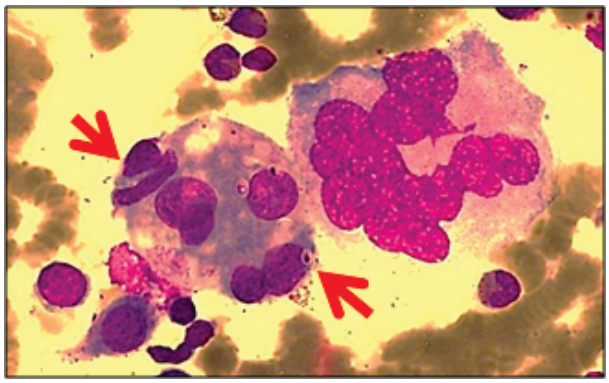

Figure 2. Bone marrow aspirate examination. The excessive hemophagocytosis activity and *Histoplasma capsulatum* inside giant histiocytes (red arrow)

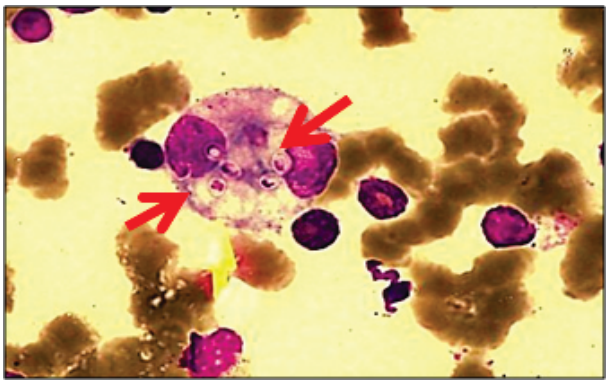

Figure 4. Bone marrow aspirate examination. The image of multiple *H.capsulatum* inside giant histiocyte histiocyte (red arrow)

To evaluate and confirm the diagnosis, the patient underwent bone marrow aspiration. The bone marrow aspiration procedure was done in the fourth day of her hospitalization. The marrow aspirate was hypercellular with normal erythropoietic activity, increased granulopoiesis, and megakaryopoiesis activity. There were dysplastic erythroid and megakaryocyte precursors. Several histiocytes with excessive hemophagocytic activity were also found (Figure 1), and they contained numerous yeast forms surrounded by a clear perinuclear zone, which was the characteristic of *Histoplasma capsulatum* (Figure 2,3,4). The diagnosis of disseminated histoplasmosis with the secondary hemophagocytic syndrome was made. The patient rejected further examination to confirm the cause of the immunocompromised state. She was hospitalized for ten days and was treated with Itraconazole 200 mg once daily for three months. After one month of treatment, her complete blood count improved without transfusions. Her hemoglobin concentration was 9.5 g/dL, leukocyte count was 3.200/µL, and platelet count was 118,000/µL. The size of her spleen also decreased to Schaffner 2. At the end of 3 months, she was fully recovered. Her complete blood count was normal, and her spleen was not palpable, indicating a decreased size. She had been under clinicians' careful observation until one year.

DISCUSSION

Histoplasma capsulatum is categorized as a dimorphic fungus. Its mycelial form can be found in soil that is contaminated with bird's and bat's dropping. The mycelial state produces spores that can be inhaled and settled in human alveoli. At normal body temperature, the spores grew into yeast form and were ingested by alveolar

macrophage. They multiply within macrophages and spread through mediastinal lymph nodes to access blood circulation, disseminating them to various organs in the body.[4,5] In case of histoplasma infection in the immunocompetent patient, this fungus could be removed and this process produces calcified granuloma in the site of infection. Histoplasmosis is primarily asymptomatic and categorized as a self-limited disease in immunocompetent individuals. In immunodeficient patients such as patients in malignancy, under immunosuppressant drugs, or HIV infection, this infection becomes severe and lethal because the cellular-mediated immunity against microorganisms is unable to develop. Patients with $CD4^+$ count < 150 cells/μL are at the most risk.[1,6]

Disseminated histoplasmosis primarily occurs in immunocompromised patients, especially in AIDS patients with very low $CD4^+$ lymphocyte count.[7] In this case, the patient had a low $CD4^+$ lymphocyte count. Still, the cause of this immunodeficiency state was not clear because the result of HIV serology, which consisted of anti-HIV-1, anti-HIV-2, and HIV-1 p24 antigen, was negative in two tests with two different methods. Unfortunately, the patient was rejected for further examination. She also did not have a medical history of taking an immunosuppressive agent. In the case of HIV infection, antiretroviral therapy should be initiated because it can restore $CD4^+$ cell count to a normal or higher level.[1] The diagnosis of disseminated histoplasmosis in this patient was established based on the bone marrow aspiration result with multiple intracytoplasmic *Histoplasma capsulatum*. Pancytopenia in this patient was caused by the extensive hemophagocytic process secondary to disseminated histoplasmosis.[3,8,9] This patient is classified into secondary hemophagocytic syndrome based on four criteria: moderate fever >38.5^{0}C, splenomegaly, peripheral blood cytopenia, and hemophagocytosis in the bone marrow. The other criteria, which are not examined in this patient are fasting triglycerides > 265 mg/dL and/or fibrinogen < 150 mg/dL, low or absence of NK-cells activity, ferritin > 500 ng/mL, elevated soluble CD25. To establish the diagnosis of the hemophagocytic syndrome, five from 8 criteria above were needed. In general, the hemophagocytic syndrome is divided into primary and secondary hemophagocytic syndrome. A genetic defect in the porfirin gene causes the primary hemophagocytic syndrome. The secondary hemophagocytic syndrome can be found in malignancy (27%), viral infection (29%), another type of infection (20%), and autoimmune disease (7%), and immune deficiency syndrome (6%).[6] In this case, the secondary hemophagocytic syndrome is caused by disseminated histoplasmosis due to her immunodeficiency state. Inpatient with pancytopenia with extensive splenomegaly, bone marrow evaluation is mandatory.

CONCLUSION

A case of a patient with pancytopenia and massive splenomegaly was reported. The final diagnosis was disseminated histoplasmosis and secondary hemophagocytic syndrome based on the marrow aspirate examination that revealed multiple intracytoplasmic *Histoplasma capsulatum* and excessive hemophagocytic activity. Disseminated histoplasmosis can be fatal in an immunodeficient patient. The cause of immunodeficiency state in this patient was still unknown because of the negative anti-HIV result. It was recommended to do a further test with an HIV RNA test.

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