Case Report

Autopsy Discoveries in Severe Malaria

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Abstract

Severe malaria is a disease caused by Plasmodium falciparum as the main cause of death in malaria. As autopsy examinations on malaria are rare in Indonesia, we report a nineteen-year-old male from Dumai, Indonesia, who died of severe malaria on November 10th, 2018, at Dumai Regional General Hospital of Riau Province. The diagnosis was concluded from autopsy, histopathology, and toxicology. This case report aimed to explain autopsy findings in severe malaria. As the result of external examination, we found some bruises on the right earlobe, lip mucosa and lower leg; excoriations on the neck, both arms and right lower leg; excoriations on the right lower leg and blood infiltration in the connective tissue on the right intercostal space. The autopsy and histopathology examination showed signs of congestion and hemozoin pigment in the brain, small intestine, liver, lung, heart, kidney, stomach and spleen. On toxicology examination, there was no narcotic substance found. Based on autopsy findings, histopathology and toxicological findings, we conclude that the cause of death, in this case, was severe malaria. Blunt violence to the ears, lips, neck, arms, and legs did not significantly cause death.
Keywords*: Malaria, Severe Malaria, Autopsy, Plasmodium falciparum.*

Penemuan Hasil Autopsi pada Malaria Berat

Abstrak

Malaria berat adalah penyakit yang disebabkan oleh Plasmodium falciparum sebagai penyebab utama kematian pada malaria. Oleh karena pemeriksaan autopsi pada malaria jarang sekali terjadi di Indonesia, maka dibuatlah sebuah laporan kasus malaria berat pada seorang laki-laki berusia 19 tahun yang meninggal di Dumai, Indonesia pada tanggal 10 November 2018 di Rumah Sakit Umum Daerah Dumai Provinsi Riau. Diagnosis disimpulkan melalui hasil pemeriksaan autopsi, histopatologi dan toksikologi. Laporan kasus ini bertujuan untuk menjelaskan hasil temuan autopsi pada malaria berat. Metode yang digunakan adalah deskriptif retrospektif. Pada pemeriksaan luar, ditemukan memar pada daun telinga kanan, selaput lendir bibir dan tungkai bawah; luka lecet pada leher, kedua lengan dan tungkai bawah kanan; luka terbuka pada tungkai kanan bawah serta resapan darah pada jaringan ikat sela iga kanan sisi belakang. Pada pemeriksaan dalam dan histopatologi ditemukan tanda-tanda kongesti serta pigmen hemozoin pada otak, usus halus, hepar, paru, jantung, ginjal, lambung dan limpa. Pada pemeriksaan toksikologi tidak ditemukan kandungan narkotika. Berdasarkan hasil temuan autopsi, histopatologi dan toksikologi, kami menyimpulkan bahwa sebab mati mayat ini akibat penyakit malaria berat. Kekerasan tumpul pada telinga, bibir, leher, kedua lengan dan tungkai tidak signifikan menimbulkan kematian.
Kata kunci: *Malaria, Malaria Berat, Autopsi, Plasmodium falciparum.*

Introduction

Malaria is an infection by protozoan parasites of the genus Plasmodium inoculated into the human host by feeding a female Anopheles mosquito.[1] According to WHO 2020, an estimated 241 million malaria occurred in 85 countries, with malaria deaths reaching 627,000.[2] Malaria occurs in most of the tropical regions of the world.[3] *Plasmodium falciparum* accounted for 279,465 estimated malaria cases in the WHO region of South-East Asia.[2] Based on 2013, Riset Kesehatan Dasar, *Plasmodium falciparum* and *P. vivax* are the most common causes of malaria in Indonesia, as much as 95%.[4] Data from Dinas Kesehatan Kota Dumai in 2016, Dumai had an Annual Malaria Incidence (AMI) of around 0,06 per 1000 population, which makes Dumai city to be a low endemicity region.[5]

Some major manifestations of severe falciparum malaria are cerebral malaria, acidosis, severe normocytic normochromic, renal failure, pulmonary edema, hypoglycemia, hypotension and bleeding/ *Disseminated Intravascular Coagulation* (DIC).[6]

Due to the rarity of clinical autopsy examination in Indonesia, particularly in malaria cases, we reported a clinical autopsy in severe malaria.

Case Description

A 19-year-old male died while attending a soldier training *Pendidikan Dasar Orientasi Lapangan Tentara Nasional Indonesia* for three months, three weeks after he began the training. He experienced dizziness, high fever and shivery. Antipyretics gave to the patient. Two days after the first symptom, the patient experienced nausea, vomiting, muscle pain, dyspnea and convulsion. The patient gave an initial treatment such as oxygen and antipyretics by health workers in the training camp.

On November 10th 2018, the patient returned to their training activity. From around 2:00 pm to 3:00 pm, the patient suddenly became unconscious. At 3:00 pm, the patient takes to the Bukit Kapur Health Center and was given action in the form of oxygen, fluids and electrocardiography examination. Then the patient refers to the Dumai Regional General Hospital. Around 5 pm, the patient was admitted to the Intensive Care Unit in that hospital but did not get better. He then died on November 11th, 2018, around 3 am. His family was suspicious that his death was due to torture during the training, so they reported the case to the police for further investigation. External examination, autopsy, toxicology, and histopathology on the corpse had done. All organ samples, including the cerebrum, aortic wall, small intestine, liver, right lung, heart, kidney, stomach, left lung and spleen, were taken.

The external examination did 12 hours post-mortem. The corpse was a male of Mongoloid race, aged around 17 to 21 years, with brown-colored skin, 168 cm in height. Black straight hair. Irises are brown with a pupil diameter of 4 mm. Eyebrows are black and grow thick with a length of 0.5 cm. Eyelashes are black and grow straight with a length of 0.4 cm. The black moustache grows sparsely with a length of 0.2 cm. The beard is black and grows sparsely, with a length of 0.2 cm. The nose is medium, the ears are oval, and the mouth is closed. The teeth were complete—r*igor mortis* found in all joints. *Livor mortis* was found on the head, neck, shoulders and back with a purplish color that did not disappear with pressure. There are bruises on the right earlobe, lip mucous membranes and lower limbs; abrasions on the neck, both arms and lower right limbs; open wounds on the lower right leg and blood infiltration in the connective tissue between the right ribs on the backside due to blunt force.

An autopsy did 30 minutes after the external examination. The brain and skull were intact, with 1445 grams weighed. There is venous congestion in the brain, and no bleeding founded. The hyoid bone, thyroid, and cricoid cartilages were intact. Thyroid color is red, chewy, red cross with 11 grams weight. The trachea has a reddish liquid. The trachea mucosal is white and does not show abnormalities. The proximal trachea has several bleeding spots, with the largest size of 0.3 cm x 0.3 cm, and the smallest are dots, covering an area of 3 cm x 1 cm. The esophagus was empty with reddish-white mucosa.

The right lung consists of three lobes, purplish red with blackish-red spots, spongy; there is reddish liquid when pressed and blood absorption between the upper and middle lobes. The left lung consists of two lobes, purplish red with bleeding spots, spongy, reddish-brown, on pressed comes out the reddish-colored liquid. Between the lobes, there are bleeding spots. The heart is brownish-red, coronary arteries were not blocked or narrowed, and the septum showed no abnormalities. There are four blood infiltration spots on the aorta. In the right atrium, there are some bleeding spots. In the right atrium on the backside, there is blood absorption. The heart weighed 222 grams.

The liver was purplish-red, the surface is slippery with sharp edges, a palpable supple, brownish-red cross-section, the structure was clear and weighed 940 grams. The spleen is brownish,

wrinkled surface, a palpable supple, purplish-red cross-section, the texture was clear, and it weighed 96 grams. Renal capsule easily detached, smooth kidney surface, brownish-red color, brownish-red cross-section. In the right kidney, there are bleeding spots and blood vessel dilation. The stomach contains blackish-green liquid; the surface is yellowish white. There are spots and dilation of blood vessels and half-digested food. The duodenum contains blackish-red liquor and dilation of blood vessels on the wall. The large intestine includes a brownish-yellow mass.

In histopathology examination, the brain was edematous, consisting of multiple necrosis focus and congested blood vessels containing erythrocytes, brownish pigments and hemozoin pigments in the erythrocytes and inside the capillary lumen. (Figure 1). The morphology of the cardiac muscle fibers showed no remarkable changes. Myocardial blood vessels widening containing erythrocytes and brownish pigments appear with the impression of hemozoin pigments inside the blood vessel lumen and in erythrocytes. The right lung was edematous. Blood vessels in the lung tissue are dilated, generally containing erythrocytes. Brownish pigments or hemozoin pigments inside the blood vessel lumen, erythrocytes, and macrophages, and multiple bleeding spots in the right lung. From the liver, there found hemozoin pigment in intravascular, erythrocytes, and macrophages. In the small intestinal tissue, the blood vessels dilated conceive erythrocytes, hemozoin pigments in the lumen of blood vessels, and erythrocytes. In splenic tissue with dilated sinuses containing erythrocytes, there is a brownish hemozoin pigment in the sinuses, inside the endothelium lining the sinuses, in the macrophages of parenchymal tissue, and erythrocytes. From the kidney, there found vascular and dilated glomerular capillaries contain erythrocytes. There was a hemozoin pigment in the vascular lumen and erythrocytes. Some epithelium tubular was necrotized (acute tubular necrosis). (Figure 2). From the toxicological examination, there was no poison found in the urine.

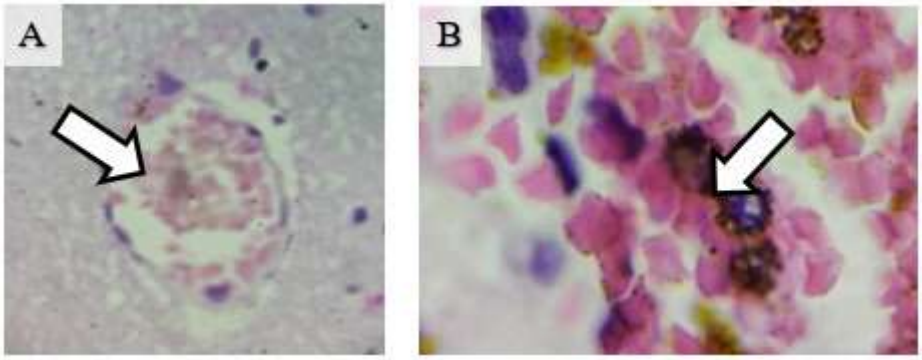

Figure 1. Histopathology Examination of Brain
A. Hemozoin malaria pigments in the brain capillaries with H&Ex10 (arrow)
B. Hemozoin Pigments Intra erythrocyte in the brain with H&Ex40 (arrow)

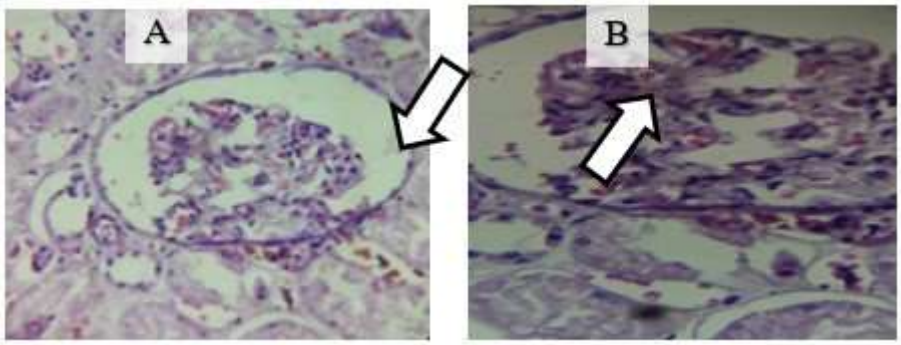

Figure 2. Histopathology Examination of Kidney
A. Erythrocytes in the glomerulus with H&Ex10 (arrow);
B. Erythrocytes in the glomerulus with H&Ex40 (arrow).

Discussion

Malaria is the infection of red blood cells by the Plasmodium parasite through the bite of *Anopheles. sp.*[7] Six species of Plasmodium can infect humans, there are *Plasmodium falciparum*, *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and the zoonotic monkey malaria species such as *Plasmodium knowlesi* and *Plasmodium cynomolgi*.[3,7] In this case, the patient attended the training in Bukit Kapur Sub-District, Dumai City. Data from the Dumai City Health Office in 2016, found that Dumai had an Annual Malaria Incident (AMI) achievement rate of 0.06 per 1000 population. It means Dumai City is a low malaria-endemic area. Several factors alter some areas to become high endemics, such as transmigration, plantation land clearing, development of shrimp ponds, and mangrove tree planting as mangrove charcoal industries.[5] Research by Sugiarto et al,[8] stated that a static pool with mud is a potential location for *Anopheles. sp.* larvae to breed. Although overall, Dumai is not a high endemic area, the training area for approximately 3 months was forests, swamps, and peatlands, which were better habitats for *Anopheles sp.* because of the large amount of water in the place. In addition, swamps and forests are better habitats for *Anopheles sp.* to lay larvae and rest places for adult mosquitoes.[9]

Plasmodium falciparum is the most cause of malaria in Indonesia, as much as 95%.[4] Death due to complications of severe malaria is generally caused by *P. falciparum* infection.[7] Several clinical stages can occur in someone infected with *Plasmodium. sp*. The stage consists of asymptomatic parasitemia, uncomplicated malaria, severe malaria, and death. Severe malaria is malaria due to *P. falciparum* infection with one or more complications. Such as cerebral malaria, severe anemia, pulmonary edema, renal failure, hypoglycemia, and convulsion.[10] Complications can occur due to the sequestration of erythrocytes that contain parasites in the microvascular of vital organs.[11] Sequestered parasites can accumulate in the blood vessels of the brain, lungs, intestines, heart, spleen, liver, muscles, and kidneys. The effect of sequestering makes hypoxia, decreases metabolite exchange, and releases inflammatory mediators. All of that can lead to disruption or failure of organ function. In the brain, this can contribute directly to cerebral edema and increased intracranial pressure.[12]

After an external examination, the cause of death still cannot be determined. We still need to find the result of the histopathology and toxicology examination. Possible causes of death by disease and poisoning still have to be considered. Histopathology examination is crucial in this case; it was carried out using the hematoxylin and eosin staining method to view malaria pigments. Staining can be done through 4 methods, hematoxylin and eosin staining, hematoxylin and eosin staining after bleaching, yzer staining, and fontana-masson staining to obtain a higher level of confidence. Malaria pigment in this patient was found in blood vessels, small intestine, brain, liver, lung, heart, kidney, stomach, and spleen. The cerebrum experienced edema and dilated cerebral blood vessels containing erythrocytes. We found brownish pigment and hemozoin in the lumen of blood vessels and erythrocytes. The findings are in accordance with cerebral malaria signs, where the malaria pigment is only found in the lumen of blood vessels and has never been inside brain tissue. There were no abnormalities in heart tissue. The blood vessels in muscle tissue were dilated with erythrocytes inside, and malaria pigments were found in the blood vessel lumen and erythrocytes. That is similar to the case stated by Afandi et al[13] in 2008, who discovered malaria pigments in the heart muscle but found no abnormalities in the heart muscle, such as thickening of the coronary arteries or signs of infarction.[13] The blood vessels in the lung tissue were dilated, generally containing erythrocytes. Brownish pigments appeared to be the appearance of hemozoin pigments inside the blood vessel lumen, in erythrocytes, and macrophages. There is a bleeding focus found in the right lung.

The liver macroscopically was purplish-red. The surface was slippery, with sharp edges, supple touch, and a brownish red-cross section. On histopathologic examination, widening of the sinuses containing erythrocytes was obtained. Hemozoin pigments are found in intravascular, erythrocytes, and macrophages. This result was in accordance with Hathila et al[14] in 12 cases of deaths due to malaria, malaria pigments were found in all cases. A study by Jodphur[13] also revealed that liver histopathology in *P. falciparum* malaria patients had malaria pigments (90%). In the small intestine was dilation of blood vessels containing erythrocytes, malaria pigment in the lumen, and erythrocytes. In the spleen, there was a widening of the sinuses containing erythrocytes. Malaria pigments were found in the sinuses, endothelial sinuses, and parenchymal macrophages. There were no signs of an enlarged spleen. Enlargement of the spleen

is common in chronic malaria, children, and semi-immune people. Research by Hathila, et al[14] in India found an enlarged spleen in all cases of death due to severe malaria, which was 12 cases, in contrast to the case report by Afandi et al[13] who did not find an enlarged spleen.[13,14] Plasmodium falciparum causes infected erythrocytes to attach to capillary and venular endothelium (cytoadherence), to uninfected erythrocytes (rosetting), and other infected erythrocytes (agglutination). These three things cause the sequestration of erythrocytes in the microcirculation of the brain and other organs so that they avoid destruction by the spleen.[15] Different in endemic areas, where the body's abnormal immune response due to repeated parasitic infections can cause spleen enlargement.[12] Vascular and dilated glomerular capillaries contain erythrocytes. There is a hemozoin pigment in the vascular lumen and erythrocytes. Some are tubular, with the epithelium experiencing necrosis. Acute kidney failure is common in severe falciparum malaria. The pathogenesis of renal failure is still unclear but may be related to sequestration, and agglutination interferes with microcirculation flow and metabolism. Clinically and pathologically, the syndrome manifests as acute tubular necrosis.[10]

Post-mortal diagnosis of severe malaria is determined by the presence of parasites and/or malaria pigments in organs.[13] Giemsa staining and examination of polymerase chain reaction (PCR) allows the pathologist to confirm the diagnosis and determine the severity of the disease.[16] The PCR method has better sensitivity than the Giemsa smear examination but requires a more expensive cost and a longer time to proceed. The PCR method is recommended if possible because PCR is a valid method for confirming diagnosis after death.[17]

Cerebral malaria as a cause of death through post-mortem examination must be based on the finding of erythrocytes containing mature *P. falciparum* (mature trophozoite or schizont) or the discovery of malaria pigments in the brain. In this case, we found pulmonary edema and hemozoin pigment in the brain from a histological examination, so we classified the patient as a severe malaria. Malaria pigment was also found in the brain. Still, the patient was diagnosed with severe malaria because the discovery of the malaria pigment in the brain can provide various symptoms depending on the density of its sequestration. At the same time, death can be due to other organ failures.[13]

Learning from this case report, it is still possible to find malaria sufferers in areas with low AMI rates. Not just because the AMI rates are low, then we ignore the suspicion of an incidence of malaria. Especially when there are supporting clinical symptoms such as chills, headaches, dizziness, anorexia, fever, and muscle aches as found in this case report.

This case report reveals the importance of carrying out a medicolegal autopsy which is generally performed in an unnatural manner of death. This is based on the fact that death from severe malaria is categorized as a natural death. Medicolegal autopsies were initially carried out because bruises and abrasions were found on the bodies as initial evidence of alleged abuse. So that the autopsy act becomes a tool to reveal that the victim died because of the disease not because of the persecution.

Conclusions

Based on the autopsy, histopathology and toxicology examination, the cause of death of this patient was due to severe malaria following the discovery of malaria pigments in blood vessels in the small intestine, brain, liver, lung, heart, kidney, stomach, and spleen. Blunt force on the ears, lips, neck, arms, and legs did not significantly cause death. From the toxicology examination of urine, no toxic content of narcotics was found. Through this article, the authors suggest that a histopathological examination should be carried out using the fontana-masson staining method if you find a similar case because it has a higher degree of confidence. If you want to confirm the diagnosis and the severity of the disease better, you can do it with a PCR examination, but with the consequence that it is more expensive and the examination process takes longer.

Conflict of Interest

The authors declare that they have no competing interests.

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