Case Report

Case Report: Multisystem Langerhans Cell Histiocytosis (LCH) and Myelodysplastic Syndrome (MDS) in a 13-Month-Old Female

Laporan Kasus: Multiple Langerhans Cell Histiocytosis (LCH) dan Myelodysplastic Syndrome (MDS) pada Anak Perempuan Usia 13 Bulan

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ABSTRACT

Langerhans Cell Histiocytosis or LCH and Myelodysplastic syndrome or MDS in children are rare diseases. It is estimated to be 1 to 4 cases per 1 million population and less than 5% of hematologic cases. MDS in LCH can occur due to genetic predisposition, impaired cytokine production, or secondary to chemotherapy. The article reported a patient case of a 13-month-old female who came to hospital with paleness since two weeks before admission. The patient also experienced skin redness, abdominal distention, and weight loss. From the physical examination, anemia, maculopapular rash, and hepatosplenomegaly were obtained. From the laboratory test, anemia of hypochromic anisopoikilocytosis, monocytosis, thrombocytopenia, and hypoalbuminemia were obtained. On examination of bone marrow aspiration, MDS with Refractory Cytopenia of Childhood type or RCC was obtained. Positive results confirmed the diagnosis of Langerhans Cell Histiocytosis on CD68 and S100 in histopathological examinations.

Keywords: Langerhans cell histiocytosis, myelodysplastic syndrome

ABSTRAK

Langerhans Cell Histiocytosis (LCH) dan Myelodysplastic syndrome (MDS) pada anak merupakan penyakit yang langka. LCH diperkirakan terjadi pada 1 sampai 4 kasus per 1 juta populasi dan kurang dari 5% dari kasus hematologi. MDS pada LCH dapat terjadi karena predisposisi genetik, gangguan produksi sitokin, ataupun sekunder akibat kemoterapi. Artikel melaporkan kasus pasien anak perempuan usia 13 bulan datang ke rumah sakit dengan keluhan pucat sejak 2 minggu sebelum masuk rumah sakit. Pasien juga mengalami kemerahan pada kulit, pembesaran perut dan penurunan berat badan. Pemeriksaan fisik didapatkan anemia, ruam makulopapular dan hepatosplenomegali. Pemeriksaan laboratorium didapatkan anemia hipokrom anisopoikilositosis, monositosis, trombositopenia, dan hipoalbuminemia. Pada pemeriksaan aspirasi sumsum tulang didapatkan Myelodysplastic Syndrome tipe Refractory Cytopenia of Childhood. Diagnosis Langerhans Cell Histiocytosis ditegakkan dengan adanya hasil positif pada CD68 dan S100 dalam pemeriksaan histopatologi.

Kata Kunci: Langerhans Cell Histiocytosis, Myelodysplastic Syndrome

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INTRODUCTION

Langerhans cells are dendritic cells with an irregularly shaped nucleus. Typically, Langerhans cells reside in the epidermis, oral and vaginal mucosa, and lungs. Langerhans cells originate from the hematopoietic system in the bone marrow. Langerhans Cell Histiocytosis (LCH) emerges due to an incorrect differentiation process of dendritic cell precursors. This disease can be distinguished by clinical characteristics and histopathological staining with specific surface markers (1). Langerhans Cell Histiocytosis is a clonal disease of a rare monocyte-macrophage system, characterized by uncontrolled proliferation and accumulation of dendritic cells (2). LCH has two to five cases per 1 million cases per year with a peak case at the ages of 1 to 4 years old (3). In LCH, many Langerhans cells are produced and accumulate in certain parts of the body, causing organ damage. Circulating cells with the BRAF V600E gene mutation are associated with a high risk as well as a two-fold increased risk of recurrence (2). The clinical manifestations of LCH are usually the appearance of lesions on the skin or bone. Systemic symptoms such as fever, weight loss, diarrhea, edema, dyspnea, polydipsia, and polyuria can also occur (1). In establishing the diagnosis of LCH, histopathological, and immunophenotyping examinations from the biopsy of the lesion tissue and immunohistochemistry are required (4,5). Langerhans cells migrate to lymph nodes, and present the antigen to T cells and can be stained to identify. The CD68 and S100 are important markers for establishing LCH. Characteristic immunophenotype of LCH includes expression of S100 protein and CD68 (1).

Myelodysplastic syndrome (MDS) is a clonal hematopoietic disorder characterized by peripheral cytopenia, ineffective hematopoiesis, and an increased risk of leukemia progression. Myelodysplastic syndrome in children is a rare disease with 1 to 4 cases per 1 million population (6). Myelodysplastic syndrome cases in children are less than 5% of all other hematologic cases (6,7). MDS cases in children are generally associated with exposure to cytotoxic agents, congenital bone marrow failure, or genetic predisposition. Refractory Cytopenia of Childhood (RCC) is the most common subtype of MDS in children characterized by persistent cytopenia with <5% blast cells in the bone marrow, <2% blast cells in peripheral blood, and dysplasia feature (6). This paper reports a case of a 13-month-old female with MDS in Multisystem Langerhans Cell Histiocytosis.

CASE

A 13-month-old female came with the main complaint of pale for two weeks before being admitted to the hospital. The patient also has reddish spots on the scalp, ears, body, and palms followed by brownish-yellow scales since five months ago. The patient's ears also had yellow discharge since three weeks ago. The patient's stomach looked bigger than other babies of her age and felt hard, especially in the past two months. The patient felt intermittent fever and decreased appetite for the past five months. The patient had been treated with ointments and antibiotics, but there was no significant improvement in her condition. Then, she was referred to Dr. Saiful Anwar Hospital, Malang, in August 2019.

Figure 1. Clinical appearances

Note: A. Conjunctival anaemia, B. Reddish spots in palm, C. Yellowish ear discharge and reddish spot on ear, D. Reddish spot on scalp, with brownish-yellow scales, E. maculopapular rash, purpura, multiple papules, crusted and yellowish-white scale in stomach, F. Hepatosplenomegaly

The patient's physical examination indicated consciousness, respiratory rate of 52 breaths/minute, pulse rate of 168 beats/minute, a temperature of 37.8°C, and 98% of SpO₂ with a nasal cannula. The patient's anthropometric assessment suggested: 7.1 kilograms bodyweight, 72 cm body length, 44 cm head circumference, 13 cm mid-upper arm circumference, with an underweight status of <-3SD. Head and neck examination also indicated conjunctival anemia, maculopapular rash, purpura, multiple papules, varied size and shape, firm borders, irregular edges, erosions with erythema, crusted impetigo, and yellowish-white scale on the scalp, palms, as well as stomach. Meanwhile, the diascopy suggested non-blanchable erythema and a lump in the neck. The chest movement was symmetrical and normal, with clear breathing sounds and no retractions. Based on the abdominal examination, the abdomen was convex with hepatomegaly and splenomegaly (Schuffner II) (Figure 1, E & F).

The complete blood count (Table 1) and blood smear revealed that the patient was hypochromic anisopoikilocytosis anemia, monocytosis, and thrombocytopenia. Anemia and thrombocytopenia were identified in the patient, which could be caused by bone marrow failure (2). Monocytosis that happened was probably caused by the stimulation of the Monocyte Colony Stimulating Factor that co-occurs with histiocyte proliferation (1). The results of the blood chemistry test, suggested a decrease in Serum Iron (SI), Total Iron Binding Capacity (TIBC), and hypoalbuminemia. The decreasing SI and TIBC occur as a result of the anemia of chronic disease. The hypoalbuminemia was caused by the infiltration of histiocytes to the liver, resulting in impaired liver function.

Table 1. Complete blood count and blood chemistry

Parameter	Result	Unit	Reference
Hemoglobin	7,20	g/dL	10,7 – 13,1
Red Blood Cell Count	2,50	10 ⁶ /μL	3,6 – 5,2
White Blood Cell Count	6,54	10 ³ /μL	6,0 – 17,5
Hematocrit	22,30	%	35 – 43

Table 1. Complete blood count and blood chemistry

Parameter	Result	Unit	Reference
Platelet Count	90	$10^3/\mu\text{L}$	229 – 553
MCV	89,20	fL	74 – 102
MCH	28,80	pg	23 – 31
MCHC	32,30	g/dL	28 – 32
RDW	18,80	%	11,5-14,5
Differential Count:		%	
Eosinophil	0		1-3
Basophil	0		0-1
Stab	-		3-5
Neutrophil			54-62
Lymphocyte	47		25-33
Monocyte			3-7
	37		
	16		
Reticulocyte		%	0,2 – 2,8
	1,77		
Immature Platelet Fraction		%	1,1 – 6,1
	5,2		
Iron		$\mu\text{g/dL}$	25 – 101
	19		
TIBC		$\mu\text{g/dL}$	228 – 428
	120		
Transferrin Saturation		%	16 – 45
	16		
AST/SGOT		U/L	<56
	30		
ALT/SGPT	8	U/L	<39
Albumin		g/dL	3,8 – 5,4
	2,59		
Random Blood Sugar	85	mg/dL	60 – 100
Urea		mg/dL	11 – 36
	13,10		
Creatinine		mg/dL	<0,41
	0,18		
Uric Acid	2,6	mg/dL	1,8 – 5
LDH		U/L	<850
ALP	282	U/L	<673
	289

Figure 2. Bone marrow aspiration results

Note: A. Bone Marrow showed hypercellularity in 10x magnification, B. Dysgranulopoiesis as dysplasia feature in 100x magnification

Bone marrow aspiration examination showed hypercellular features, myeloid to erythroid ratio(M:E) = 2:1, increased erythropoiesis activity, granulopoiesis, megakaryopoiesis, dyserythropoiesis, dysgranulopoiesis, dysmegakaryopoiesis, positive Fe reserves, with megaloblastic changes in the three types of hematopoietic systems (Figure 2). It indicated RCC as subtype of MDS in children based on WHO 2016 criteria: persistent cytopenia with <5% blast cells in the bone marrow, <2% blast cells in peripheral blood, and dysplasia feature (6).

Figure 3. Imaging of Thorax and Abdomen

Note: A. Chest X-Ray: increased bilateral vascular infiltrates showed pulmonary edema, B. Abdominal Ultrasound: Hepatomegaly and ascites C. Abdominal Ultrasound: Splenomegaly

The results of the thorax radiograph revealed pulmonary edema. There were no lytic bone lesions on the patient. Meanwhile, ultrasonography results showed the existence of ascites and hepatosplenomegaly (Figure 3).

Figure 4. Histopathology reports from skin ulcer

Note: A. cell proliferation with an oval-shaped and reniform-shaped nucleus (in 100x magnification), B.Positive result of CD68 showed Langerhans cell (in 400x magnification), C. Positive result of S100 in Langerhans cell (in 400x magnification)

Anatomical pathology biopsy from skin tissue indicated the existence of skin ulcer, cell proliferation with an oval shaped and reniform-shaped nucleus with nuclear groove, vesicular chromatin, pale cytoplasm with the distribution

of eosinophils in inflammation, lymphocytes, and neutrophils (Figure 4). The immunohistochemical examination result indicated a positive result of CD68 and a strong positive result of S100 protein on the cytoplasmic membrane of tumor cells. The conclusion of the immunohistochemical examination is following Langerhans Cell Histiocytosis and meet the criteria for diagnosis for LCH.

Based on the patient's medical history, physical examination, laboratory examination, radiological examination, biopsy, and immunohistochemistry, it can be concluded that the patient encountered Multisystem Langerhans Cell Histiocytosis or MS-LCH (affect skin, lung, liver, ear, hematopoietic system) and MDS.

DISCUSSION

This case report presented a 13-month-old patient diagnosed with MS-LCH (skin, lung, liver, ear, hematopoietic involvement) with MDS, which was based on the patient's history, physical examination, laboratory, radiology, and histopathology. Myelodysplastic syndrome is a collection of symptoms due to clonal hematopoiesis disorders characterized by peripheral cytopenia, ineffective hematopoiesis, and an increased risk of progression to leukemia. MDS cases that occurred in children are less than 5% of all other hematologic cases (6,7). MDS cases in children are usually associated with exposure to cytotoxic, congenital bone marrow failure, or genetic predisposition. Refractory Cytopenia of Childhood the most common subtype of MDS in children. Refractory Cytopenia of Childhood is defined as the presence of persistent cytopenia with <5% blast cells in the bone marrow, <2% blast cells in peripheral blood, and dysplasia feature (6).

Langerhans Cell Histiocytosis is a disease caused by the disruption in the differentiation process of dendritic cell precursors or the transformation of Langerhans cells. Langerhans Cell Histiocytosis had two to 10 cases per 1 million children under 15 years old (1). Multisystem cases of LCH are common in children under one year old (4). In LCH, mutations in the somatic gene of BRAF V600E occurred in 57%, and MAP2K1 gene mutations occurred in approximately 75% of patients with neoplastic processes. Systemic symptoms such as fever, weight loss, diarrhea, edema, dyspnea, polydipsia, and polyuria might occur. In LCH, the involvement of specific organs at the time of diagnosis can determine high or low-risk disease classification. The risk classification is high if the organs are involved, such as the liver, spleen, and bone marrow. Meanwhile, the risk is low if the organs are involved, such as the skin, bones, lungs, lymph nodes, and pituitary gland. The patient might have a complaint from one organ system or several organs (1,8). The diagnosis of LCH is based on the histopathological examination, and immunophenotyping from tissue biopsy is to find CD1a

and/or CD207 (Langerin) on the surface of LCH cells or the presence of S100 protein and CD68, which is detected by immunohistochemistry (2,4,5).

The patient in this report was 13 months old that concurred with the age of the most common occurrence of LCH in children. Langerhans Cell Histiocytosis can affect all ages, with the peak of the most common period of 30 months. Fever in the patient occurred due to a decrease in the immune system in LCH. Lump on the patient's neck, scaly skin, and crusting was the result of the spread of LCH to the lymph nodes and skin. The discharge from the patient's ear was one of the clinical manifestations of LCH (1). Anemia and thrombocytopenia in this patient due to LCH might lead to bone marrow failure (1,9). The decreased levels of SI and TIBC occurred due to anemia of chronic disease (10). The infiltration of LCH cells to the liver and spleen causes hepatomegaly and splenomegaly, in addition to causing organ enlargement, it can also result in impaired liver function, such as hypoalbuminemia (11). In this patient, LCH involving multiple organ like skin, lung, liver, ear and hematopoietic system. Several cases of LCH have been reported progressed into haematological disorders, such as MDS. In a 2017 study, there were cases of LCH that were correlated with MDS, and it is suspected that both of those occurred due to disruption of cytokine production, which resulted in reactive histiocytes and abnormalities of the hematopoietic system (12).

In this patient correlation between LCH and MDS still unclear. Several possible theories enable the correlation between LCH and MDS. LCH and MDS could occur simultaneously, or there was a suspicion that LCH can risk developing MDS. Genetic predisposition that occurred between MDS and LCH could be one of the possibilities. There was speculation that LCH and the risk of haematological malignancies stem from chromosome seven abnormalities. Abnormality on chromosome 7 has been documented in LCH, MDS, and AML (13). MDS could occur secondarily due to chemotherapy (etoposide and vinblastine) from LCH (14,15). Unfortunately, patient's condition deteriorated rapidly and passed away before receiving chemotherapy. The cumulative risk of MDS increased by 0.25–2% per year after starting the therapy and continued six to eight years after the treatment. Another possibility was the correlation between MDS and LCH is caused by the production of anomalous cytokines, causing the histiocyte cells to become reactive and disrupt the hematopoietic system (15).

This study reported a 13 months-old female patient diagnosed with MS-LCH (skin, lung, liver, ear, hematopoietic involvement) with MDS. The patient was in a high-risk state, and had a poor prognosis due to multisystem LCH. Even though, MDS that occurred in LCH remained unclear, there are several possible theories that enable the correlation, like genetic predisposition, impaired cytokine production, and chemotherapy side effects.

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