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CONTENTS

RESEARCH

LITERATURE REVIEW

CASE REPORT

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PAGE 121
2018 Nov; 25(1): 1-
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LEUKEMIC PHASE OF MALIGNANT LYMPHOMA IN CHILDREN

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ABSTRACT

Leukemic phase of malignant lymphoma is a group of lymphoid malignancies typically localized in lymph node and present typical clinical features such as lymphadenopathy with irregular distribution. It can manifest as an extranodal disorder infiltrates the bloodstream (leukemic phase). Lymphomas are differentiated into Hodgkin and non-Hodgkin. The presentation of Reed-Sternberg (RS) cells in histological evaluation establishes Hodgkin lymphoma. A number of classification systems have been used before the publication of Revised European American Lymphoma (REAL) classification in 1994 which includes all lymphoid and lymphoma malignancies according to typical histology, morphology, immunophenotype, genetic, and clinical manifestation. A highly proliferative and fatal malignant lymphoma with leukemic phase case in 13 years and a one-month-old male was reported. The diagnosis was established based on marble-sized lymph nodes enlargement that increased in size, two weeks after initial identification on the neck, head, and inguinal regions and followed by lymphadenopathies in submental, right submandibular, preauricular and right inguinal region. No fever history of this patient or malignant history among his family was found. Laboratory findings included WBC of 26,050/µL, Hb 9.6 g/dL, and PLT 16,000/µL. Peripheral blood smear results indicated suspected leukemic phase of malignant lymphoma DD/ALL. Bone marrow aspiration showed leukemic-phase of malignant lymphoma with bone marrow infiltration. Cytological evaluation of Fine Needle Aspiration (FNA) identified atypical round nucleated cells with nucleus size mostly larger than the mature lymphocytes, minimum cytoplasm, diffuse erythrocyte as background, a conclusion was malignant lymphoma.

Key words: Leukemic phase, non-Hodgkin malignant lymphoma

INTRODUCTION

Leukemic phase of malignant lymphoma is a group of solid lymphoproliferative malignancies affecting the lymph nodes. This condition may show a typical clinical manifestation of lymphadenopathy with irregular pattern spread pattern. This condition can also manifest as an extranodal disease infiltrating into the bloodstream that gives leukemic representation in peripheral blood.[1-4]

Malignant lymphoma is differentiated into two main groups, i.e. Hodgkin lymphoma and non-Hodgkin lymphoma. The Hodgkin lymphoma condition is established based on the presence of Reed-Sternberg cell that commonly came from T lymphocytes. Meanwhile, the non-Hodgkin lymphoma commonly originates from precursor cells of B lymphocytes (85%). The non-Hodgkin lymphoma is known to be very progressive and usually called B-lymphoblastic leukemia/ lymphoma/B-LBL, while only 15% is originated from Natural killer cell/T cell.[1-4,5]

The non-Hodgkin lymphoma prevalence is three percent more common than the prevalence of Hodgkin lymphoma and tends to occur in young adults, male compared to female. Immunodeficiency state (hereditary or acquired) is the precipitating factor of B cell lymphoma especially lymphoma caused by an oncologic virus such as Epstein Barr Virus/EBV, Human T lymphotropic virus Type I/ HTLV-1 and Acquired Immunodeficiency Syndrome/AIDS. Hepatitis C virus is proposed for being one of Non-Hodgkin lymphomas risk factors. Epstein Barr virus is found in more than 50% of cases of Hodgkin lymphoma but the pathogenesis of this condition has not been clearly defined.[1,4,6]

Leukemic phase of malignant lymphoma comprises about 1% of several lymphoma cases. The blood smear evaluation picture of a leukemic phase of lymphoma depends on the type of lymphoma, e.g. cleaved follicular lymphoma cells can be found in blood smear picture of mantle cell lymphoma patients. Lymphadenopathy and splenomegaly can be found in this type of lymphoma. Lymphoma types can be determined based on cytologic examination, immunophenotyping, histologic and cytogenetic (molecular genetic) examination. Cytologic examination such as trephine biopsy and immunophenotyping can be very helpful in establishing the leukemia diagnosis of B lymphocyte, T lymphocyte, and NK cell. Those examinations can also be useful to differentiate between Acute

Lymphoblastic Leukemia (ALL) and lymphoblastic lymphoma involving lymph nodes and also to give a prognostic picture and monitor Minimal Residual Disease (MRD) in lymphoproliferative disease. The cytogenetic or molecular genetic examination can be used to determine neoplastic properties based on particular cytogenetic picture characterizing a specific type of leukemia or lymphoma.[1,7]

In 1994, it had been released the Revised European American Lymphoma (REAL)/WHO involving all types of lymphoid malignancies (Table 1).

Table 1. Classification of lymphoma neoplasm based on REAL and WHO 1994.[1,2,4]

Lymphoid neoplasms
Precursor B-cell neoplasma
B-cell acute lymphoblastic/lymphoma (B -ALL)
Peripheral B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic and nodal marginal zone lymphoma Mantle cell lymphoma
Extranodal marginal zone lymphoma
Mantle cell lymphoma
Follicular lymphoma
Marginal zone lymphoma
Hairy cell leukemia
Plasmacytoma/plasma cell myeloma
Diffuse large B-cell lymphoma
Burkitt' s lymphoma
Precursor T-cell neoplasms
T-cell acute lymphoblastic leukemia/lymphoma (T -ALL)
Peripheral T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
Large granular lymphocytic leukemia
Mycosis fungoides/sezary syndrome
Peripheral T-cell lymphoma, unspecified
Anaplastic large-cell lymphoma
Angioimmunoblastic T -cell lymphoma
Enteropathy-associated T-cell lymphoma
Panniculitis-like T-cell lymphoma
Hepatosplenic d t -cell lymphoma
Adult t-cell leukemia/lymphoma
Extranodal NK/t -cell lymphoma
NK-cell leukemia
Hodgkin lymphoma
Classical subtypes
Nodular sclerosis
Mixed cellularity
Lymphocyte-rich
Lymphocyte depletion
Lymphocyte predominance

Early diagnosis can be made based on accurate excision biopsy examination of lymph node sample. After establishing the diagnosis, determining the stage of disease can be made because it determines the patient's therapy and prognosis. Stage of the disease commonly established based on Ann Arbor criteria with the Cotswold revision (Table 2).[6]

CASE

A boy, 13 years one-month-old lived in Polopo admitted to the Dr. Wahidin Sudirohusodo Hospital on February 12, 2014 (Figure 1). He was treated in neurosurgery division with the diagnosis of bilateral collie tumor. On February 25, 2014, the patient had therapy under collaboration with the pediatric division and the diagnosis was a right retrobulbar tumor and malignant lymphoma. Main complain were Lumps in neck, eye, head and groin area.

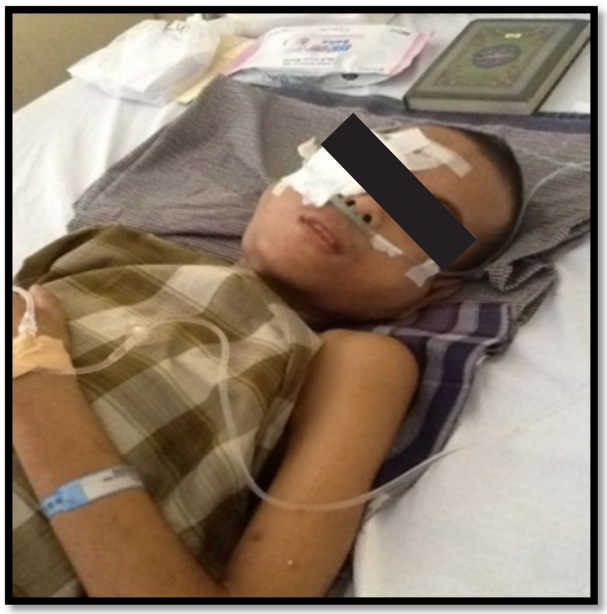

Figure 1. Malignant lymphoma patient

Patient admitted to hospital with a complaint of lumps that began to appear first on his neck, the size of a marble and grew slowly in two weeks. Lumps then appeared under both ears about a peanut size, and after that, it appeared in his right eye, head and groin. Those lumps became larger in one month. The patient did not complain of any fever at the time. However, he experienced a fever for a month. He had no seizure, no cough, no dyspnea, no vomiting, but a loss of appetite.

The patient was hospitalized in Palopo Hospital for about four days. He got intravenous infusion, antipyretics and blood transfusion, three times, but his family was not sure about the number of blood

Table 2. Determining stage of malignant lymphoma disease based on Ann Arbor criteria.[6]

Stage	Definition
I	Involveme nt of single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes are lateralized)
III	Invo lvement of lymph node regions or structures on both sides of the diaphragm
III_1	With or without splenic, hilar, celiac, or portal nodes
III_2	With para - aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site
	Annotation : No symptoms
	Fever, drenching sweats, or weight loss

Note: each stage is differentiated into category A if there is no systemic symptom and B if there is systemic symptom i.e. fever ≥ 38° C without a known cause, night sweat or loss of body weight ≥ 10% in 6 months.

transfusions. He was then referred to the Wahidin Sudirohusodo Hospital. The family's malignancy history was unknown.

The maternal pregnancy history was a term pregnancy. A midwife assisted the delivery process. The amniotic fluid volume was unknown. The baby spontaneously cried with a baby body weight of 3000 gram and unknown baby body length. The baby got breast milk and vaccinations.

Physical examination

General condition: severely ill, compos mentis, nutritionally adequate; Body weight 48 kg, blood pressure: 120/70 mmHg, pulse rate: 80x/minute. Respiratory rate: 28x/minute, body temperature: 36.50C. Lymphadenopathy: submental: 3 lymph nodes with the sizes of 1x1 cm, 2x2 cm, and 1.5x1.5 cm; Right submandibular: 1 lymph node with the size of 5x4 cm; Right preauricular with the size of 8x7 cm; Left preauricular with the size of 10x9 cm; Retroauricular with the size of 0.5x0.5 cm; Right inguinal: 4 lymph nodes with the sizes of 3x3 cm, 3x2 cm, 2x2 cm, and 1x1 cm. Thorax: breath sounds: vesicular, rhonchi-/-, wheezing-/-. Heart sounds: first and second heart sounds were clear and regular, no murmur. Abdomen: normal bowel sound, peristaltic (+). A liver was palpable on 5 cm below right costal margin with soft consistency, smooth surface, sharp border, and no tenderness. The spleen was palpable on Schüffner II with tender consistency. Extremities: no abnormality.

Head CT Scan Examination

The examination was done on February 11, 2014, using axial cut orbital CT Scan without contrast. The result suggested that, right retrobulbar mass suggesting hemangioma and multisinusitis.

Cytology Examination/Fine Needle Aspiration (FNA)

Fine Needle Aspiration (FNA) result on February 12, 2014 (Figure 2): Clinical information: a bilateral collie tumor. Lumps in both submandibular side with the sizes of 4 cm and 2 cm masses in the right side, while 4 cm mass in the left side. Conclusion: Malignant lymphoma. Suggestion: Excisional biopsy confirmation examination.

Hematology Examination

Complete blood count was measured using hematology analyzer (Table 3).

Blood smear evaluations were done on February 27, 2014, and March 12, 2014. The smears showed monotone pleomorphic mononuclear cells suggesting lymphoblasts (Table 4, Figure 3, 4).

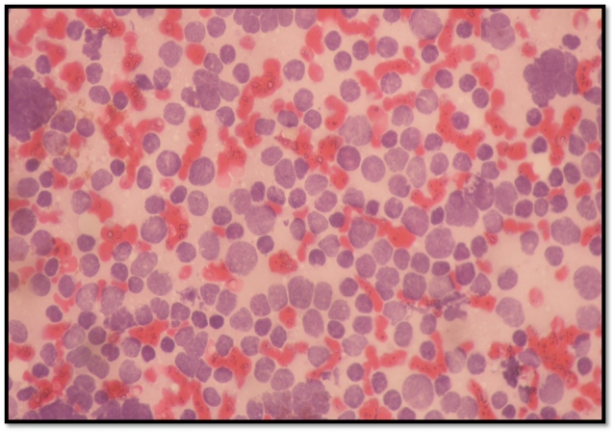

Figure 2. Smear preparation of left collie, done on February 12, 2014, consisting of atypic cells with a round nucleus and minimal cytoplasm. The nucleus size was larger than the mature lymphocyte size. Those cells were spread widely in the midst erythrocyte background.

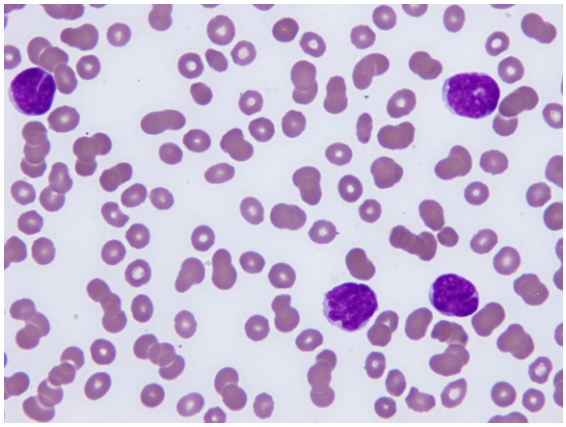

Figure 3. Blood smear evaluation on February 27, 2014, found lymphoblast. (MGG staining, 100x magnification)

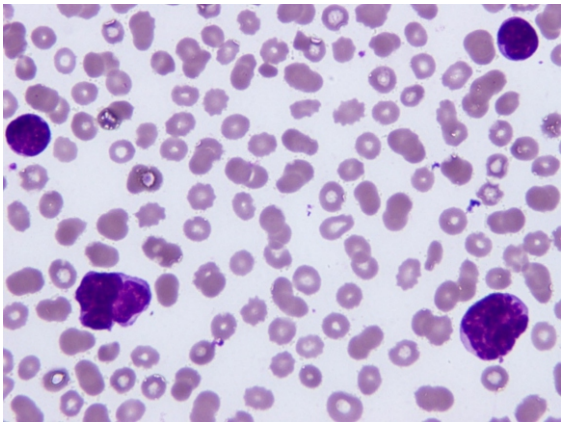

Figure 4. Blood smear evaluation picture on March 12, 2014, found monotonous lymphoid series with lymphoblast (+) (MGG staining, 100x magnification).

Table 3. Complete blood count results using hematology analyzer

CBC	Date			
	26-02-2014	27-02-2014	12-03-2014 Post-transfusion	15-03-2014 Post-chemotherapy
Hemoglobin(HGB)	9.7 g/dL	9.6 g/dL	14.4 g/dL	8,4 g/dL
White blood cell count	13.200/µL	26.050/µL	17.150/µL	300 /µL
Red blood cell count	$3.31x10^6$/µL	$3.32x10^6$/µL	$5.01x10^6$/µL	$2,78x10^6$/µL
Hematocrit (HCT)	28%	28.7%	40.7%	23%
MCV	86 fl	86.4 fl	81.2 fl	84
MCH	29 pg	28.9 pg	28.7 pg	30
MCHC	34 g/dL	33.4 g/dL	35.4 g/dL	36
Platelet Count	16.000/µL	16.000/µL	43.000/µL	2.000//µL
Neutrophil	-	1.5%	-	36.3%
Lymphocyte	-	28.1%	-	52.8%
Monocyte	-	69.2%	-	3.3%
Eosinophil	0.1%	-	0.1%	2.6%
Basophil	6.7%	1.2%	-	0.01%

Table 4. Blood smear evaluation results (MGG staining)

Parameters	February 27, 2014	March 12, 2014
Erythrocyte	Normochromic normocytic anisocytosis, no inclusion body nor normoblast was found	Normochromic n ormocytic anisocytosis, no inclusion body nor normoblast was found
Leukocyte	The count seemed to be increased, dominated by lymphoid series, lymphoblast (+)	The count seeme d to be increased. There were monoton ous lymphoid cells, lymphoblast (+).
Thrombocyte	The count seemed to be very decreased with normal morphology.	The count seemed to be decreased with normal morphology
Conclusion	Suspect ALL	Suspect malignant leukemic phase of lymphoma DD ALL
Suggestion	Bone marrow aspiration	

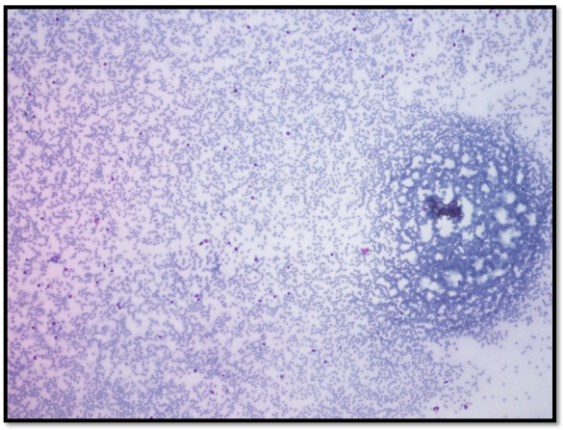

Figure 5. Bone marrow aspiration done on March 5, 2014, found lymphoblasts (MGG staining, 100x magnification)

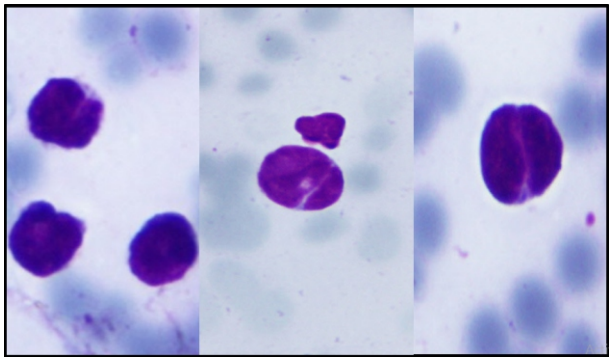

Figure 6. Bone marrow aspiration done on March 5, 2014, found lymphoblasts and lymphoma cells infiltration (MGG staining, 100x magnification)

Bone marrow aspiration done on March 15, 2014, result was attached at Table 5, Figure 5, and 6.

Clinical Chemistry Examination

Clinical chemistry examinations done on March 15, 2014, showed some increases in bilirubin level and transaminase activity level (Table 6).

Thorax Photo examination

A thorax AP photo examination had been done on March 13, 2014, with the conclusion of right pleural effusion.

DIAGNOSIS

Leukemic phase of malignant lymphoma.

PATIENT MANAGEMENT

Intravenous fluid drops (IVFD) RL: 20 drops/minute; Thrombocyte transfusions were done several times, i.e. February 26, 2014: 1 unit; February 27, 2014 : 18 units; February 28, 2014 : 12 units; March 2, 2014 : 3 units; March 8, 2014 : 19 units; March 11, 2014 : 19 units; March 12 : 19 units and March 13, 2014 : 15 units; Pack red cell transfusions were also done several times i.e. on March 7, 2014 (8640 mL); on March 9, 2014 (400 mL); on March 10, 2014 (960 mL) and on March 11, 2014 (960 mL); IVFD dextrose 5% : 20 drops/minute (March 7, 2014); Oral dexamethason tablet (started on March 7, 2014); Cyclophosphamide 1450 mg (intravenous injection) (March 8, 2014); Cytarabine 149 mg (intravenous injection) (March 8, 2014); Tramadol 20 mg (intravenous injection every 8 hours) (March 8, 2014); Oxygen supplementation using nasal cannula 2 liter/minute (March 14, 2014); Fluconazole 240 mg (intravenous injection every 12 hours) (March 14, 2014); Vincristine 2.2 mg (intravenous injection every 24 hours) (March 14, 2014); Daunorubicin 45 mg(intravenous injection every 24 hours) (March 14, 2014).

DISCUSSION

Malignant lymphoma cases accompanied with leukemic phase is a relatively rare case. It only accounts for about 1% of all malignant lymphomas, while in non-Hodgkin lymphoma it happens more

Table 5. Bone marrow aspiration results (MGG staining)

Parameters	Bone marrow aspiration evaluation
Cellularity	Hypocellular
Erythropoietic system	Decreased activity, decreased erythroid precursor cell count
Lymphopoietic system	Increased activity, found several pleomorphic mononuclear cells, lymphoblast (+) and lymphoma cells infiltration
Granulopoie sis system	Decreased activity
Thrombopoietic system	Decreased activity. No megakaryocytes were found.
Plasma cell	No plasma cell was found.
Mitosis	Present
ME Ratio	Difficult to be evaluated
Conclusion	Suspect leukemic phase of malignant lymphoma with lymphoma cells infiltration into bone marrow D D ALL

Table 6. Clinical chemistry results

Blood chemistry	Value	
	07-03-2014	15-03-2014
Random blood glucose (mg/dL)	69	164
Total Bilirubin (mg/dL)	-	15.54
Direct Bilirubin (mg/dL)	-	13.68
SGOT (U/I)	19	172
SGPT (U/I)	19	57l
Albumin (gr/dL)	-	2.1
Sodium (mmol/l)	133	124
Potassium (mmol/l)	3.5	4.1
Chloride (mmol/l)	110	101

Urine and fecal analysis done on March 11, 2014, results were within normal limit.

often, about 3% of all cases.[6] A 13 years 11 months old boy was reported a complaint of swollen start from the neck, marble size, that grew slowly in about two weeks. The lumps then appear under both ears, a peanut size and then it also grew in the right eye, head and groin that grew slowly in about one month. The patient was hospitalized in neurosurgery division, Dr. Wahidin Sudirohusoso Hospital on February 11, 2014, with a diagnosis of collie tumor.

Fine needle aspiration examination result on February 12, 2014, suggested a malignant lymphoma. The patient was treated in collaboration with the pediatric department on February 25, 2014, and the diagnosis was a retrobulbar tumor with malignant lymphoma. This case was a fatal case with unfavorable prognosis based on "Ann Arbor" staging system. This patient passed away due to already being in stage IVB, i.e. a stage when the tumor cells had involved not only many lymphatic glands but also nonlymphoid organs such as bone marrow, liver, and spleen accompanied with loss of body weight.7 Hematologic disorder found in non-Hodgkin malignant lymphoma patients consisted of normochromic normocytic anemia. An extensive bone marrow involvement could give a manifestation of anemia, leukopenia, thrombocytopenia and also a leukoerythroblastic picture as well as the leukemic phase of non-Hodgkin lymphoma with more than 5% of immature cell in peripheral blood.[6]

Blood smear evaluations were done on February 27 and March 12, 2014, results showed normochromic normocytic anemia with various sizes of atypical cleaved nucleus-lymphocyte cells suggesting lymphoblast. Meanwhile, bone marrow aspiration evaluation done on March 5, 2014, revealed an increase in lymphopoietic series activity with some mononuclear pleomorphic cells, lymphoblast, and lymphoma cells infiltration. Thrombocytopenia and neutropenia were also found because the lymphoma cells had been spread into bone marrow. There was also hepatosplenomegaly that indicates poor prognosis of this advanced disease.[1,7]

Malignant lymphoma is commonly caused by uncontrolled transformation growth of B lymphocytes. Using lymphocyte surface marker examination such as an examination that integrates fluorescence or peroxidase technique with an immunologic marker, it is possible to detect minimal involvement of clonal B cell population that cannot be easily detected using a conventional microscope.[1,7]

There was no malignancy history among the patient's family, so this condition is possibly caused by oncogenic virus infection. This infection might remain unrecognized until the clinical symptoms appeared.[1,4,6-8]

Lymphocyte differentiation and lymphocyte subtype complexities have been developed into some classifications. International experts have established a guideline to categorize malignant lymphoma in the form of Revised European American Lymphoma (REAL) classification. Based on clinical pictures and laboratory examination, this case is concluded as intermediate grade non-Hodgkin malignant lymphoma with clinical manifestations of asymmetric lymph node enlargement caused by large lymphoma cells expansion (transformed lymphocyte) and uncontrolled growth that lymph node becomes large and the cells infiltrate peripheral blood stream. This lymphoma cells commonly originate from B lymphocytes with various size and cleaved nucleus. Thrombocytopenia can be caused by lymphoma cell infiltration into bone marrow. This morphology type

is also known as "lymphosarcoma leukemic cell".[2,7]

After post-induction phase chemotherapy, bilirubin level increase on March 15, 2014. This condition showed a possibility of autoimmune hemolytic anemia process, however, it was not confirmed by Coombs test. The blood smear evaluation also showed normochromic normocytic anemia consistent with hemolytic anemia.[7] An increase in transaminase enzyme was also found on March 15, 2014, consistent with liver enlargement (about five fingers below arcus costa). This finding might be caused by an extranodal process involving abdomen especially liver and spleen. Besides, retroperitoneal and mesenteric lymph node could also be affected by this extranodal process.[1] Head CT scan result showed right retrobulbar mass suspected a hemangioma and multi sinusitis. Thorax photo found pleural effusion possibly caused by lymphoma cells spread into the mediastinum lymph node.[1]

The Hodgkin lymphoma prognosis, according to The International Prognostic Score is based on several parameters. Those parameters are albumin (less than 4 g/dL), hemoglobin (less than 10.5 g/dL), sex (male), stage IV, age (older than 45-year-old), and leukocyte count (more than 15.000/mm3). The survival rate is 90% in a patient having one or less of those factors, while the survival rate is decreased to 59% if the patient has four or more factors.[9] Non-Hodgkin lymphoma prognosis factors consist of age (more than 60 years old), hemoglobin (less than 12 g/dL), some of affected lymph node (more than 4) and increase LDH level. If the patients have one or less factor, they belong to a low risk group, while intermediate risk if they have two factors and poor risk if having more than three factors.[9] The patient, in this case, belonged to poor risk group because he had several factors, i.e. sex (male), albumin (2g/dL), Hb (<12 g/dL) and more than 4 affected lymphadenopathy.

Surgical biopsy, radiotherapy especially for Hodgkin lymphoma radiotherapies such as radioimmunotherapy (CD20 and CD22 monoclonal antibodies) and radioisotope therapy (using Iodine or Yttrium to irradiate tumor cells selectively) can be chosen as a therapeutic choice for treating the patient.[8,10] The patient, in this case, was treated with chemotherapy as the main choice because many chemotherapy regiments such as intravenous cyclophosphamide, cytarabine, vincristine, and daunorubicin had showed good effects against lymphomas.

The limitation of this case was that had not able yet to establish the type of lymphoma whether it was Hodgkin or non-Hodgkin lymphoma based on FNA cytology evaluation, only. The diagnosis of non-Hodgkin lymphoma should be established based excisional biopsy histology examination of lymph node or extranodal tissue as it is the gold standard in determining the type of lymphoma. After confirming the diagnosis, it should be continued with determining disease stage because it determines the therapy and the prognosis of the patient.[6] The excisional biopsy had not been done because the patient was already passed away on March 16, 2014, after receiving induction phase chemotherapy.

CONCLUSION

A report of a rare leukemic phase of malignant lymphoma case affected a boy 13 years one-month-old. Malignant lymphoma diagnosis was established based in the confirmative examination of FNA. Meanwhile, the leukemic phase of malignant lymphoma condition was established based on blood smear evaluation that found lymphoblast as well as bone marrow aspiration examination that found malignant lymphoma cells in bone marrow. Clinical manifestations were lymphadenopathy but no fever. Physical examination found splenomegaly. There were also normochromic normocytic anemia, thrombocytopenia, and neutropenia based on laboratory examination.

Clinical chemistry examination results found hypoalbuminemia, increase in transaminase enzyme activity and hyperbilirubinemia. The patient was passed away after receiving induction phase chemotherapy. The patient belonged to poor risk group patient with a survival rate of 59%. A definite diagnosis of Hodgkin and non-Hodgkin malignant lymphoma had not been established because the excision biopsy had not been done yet.

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