CASE REPORT

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A T-acute lymphoblastic leukemia in children with CD 117 expression: a case report

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ABSTRACT

Background: Leukemia is a group of clonal disorders originating from single cells with genetic changes in the bone marrow or peripheral lymphoid tissue. Acute T-cell lymphoblastic leukemia is estimated to be 12-15% of ALL cases. Immunotyping examination is essential in establishing the diagnosis of T-ALL, CD 1a, CD 2, CD 3 (membranous and cytoplasm), CD 4, CD 5, CD 7, and CD 8 as T- cell antigen markers. CD 33, CD 117, CD 34 and CD 56 are a myeloid-related antigen. The occurrence of co-expression of T cell markers with markers myeloid is infrequent. This study aimed to report cases of T- Acute Lymphoblastic Leukemia (ALL) in children with CD 117 expression.

Case description: A-13 years boy had a fever and bruising on the skin one year ago. Physical examination found a blood pressures 150/70 mmHg , axillary temperature 37.8°C, right and left enlargement of the glands of the neck and inguinal, enlarged liver and petechiae in both lower extremities. Complete blood tests showed leukocytosis, anemia, and thrombocytopenia. Edge blood smear suggests the presence of cigar cells, target cells and lymphoblasts > 50%. Bone marrow aspiration smear revealed lymphoblast >30% and concludes an ALL (L2). Immunophenotyping examination found CD 3, CD 5, CD 117 positively supported T-ALL with co-expression of CD 117. During treatment, the patient experienced seizures due to spontaneous intracerebral bleeding that caused the patient to die.

Conclusion: The case of a 13-year-old boy suffering from T-ALL (L2) with co-expression of CD 117 had a poor prognosis.

Keywords: Acute Lymphoblastic Leukemia, CD 117, T-ALL

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INTRODUCTION

Leukemia is a group of clonal disorders originating from single cells with genetic changes in the bone marrow or peripheral lymphoid tissue. Type of leukemia is determined based on the source of cell specification, cytology, immunohistochemistry and cytogenetic examination which is divided into acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphoid leukemia (CLL).[1,2] WHO through the 2014 World Cancer Report stated that cancer is a world health problem, especially in developing countries, it is estimated that the impact of cancer on the population in the next decades will reach 80% at more than 20 million estimated for 2025.[1,2] Some cancers can affect the general population, and leukemia can occur from the age of the child to the elderly. New cases of leukemia are enforced around 352 thousand cases are estimated worldwide in 2012, according to estimates of new cancer cases of 2.5% and 265 thousand died. Leukemia is estimated at 3% of all cases of malignancy.[1]

ALL is a malignant lymphoid cell proliferation in the early stages of differentiation. This disorder is biologically heterogeneous so that morphological, immunological, cytogenetic, biochemical, and molecular genetic characteristics are needed to establish the diagnosis or exclusion of other causes of bone marrow failure, and ultimately to determine ALL subtypes[2]

Immunological surface markers and cytoplasm cell have an important role in the classification of acute leukemia. The use of selected panel monoclonal antibodies (mAb) and the multiparameter fluorescence-activated cell sorter (FACS) development engine, are able to classify ALL B cells and ALL T cells to be several stages based on the degree of differentiation or maturation of mature B clones. ALL T cells are divided into three levels of differentiation, namely early (stage 1), intermediate (stage 2) and late (stage 3).[3]

T-Cell ALL is estimated at 12-15% of the cases of ALL that are newly diagnosed in pediatric patients, and more importantly, ALL T cells have a unique clinical and biologic picture.[3] Immunophenotypic studies in T-ALL showed that cortical and mature subtypes were present in the majority of cases, showing mediastinal involvement in very high frequencies (more than 90%).

In contrast, T-ALL cortical subtypes in 50% of cases, pre-T in 25% of cases and mature T in the remaining 25% showed mediastinal involvement of 60-70%. In the clinical setting, the two groups of subtypes (Pre T-cell and T Mature cell) were

dominant in men. Both of subtypes also showed a diagnostical central nervous system (CNS) involvement with a similar frequency (5-10%).[4] Immunotyping examination with flowcytometry shown VING CD1a, CD2, CD 3 (membranous and cytoplasmic markers), CD 4, CD 5, CD 7, and CD 8 T cells as antigen markers. CD 33, CD 117, CD 34 and CD 56 as an antigen myeloid related was found to be expressed in T-ALL cells. However, the simultaneous expression of all these markers in one patient was never reported previously.[5] CD 117 is a transmembrane protein receptor coded by c-kit oncogenes. This marker is a stem cell ligand that is an important regulator of hematopoiesis. CD 117 presents in about 4% of normal bone marrow mononuclear cells and appears in AML, CML with blast crisis, as well as more significant in ALL.[6]

Abnormalities of several organs or tissues can occur in ALL, although it is a primary abnormality in the bone marrow and peripheral blood, because abnormal cells can infiltrate several organs. The duration of symptoms in children with ALL varies from a few days to several months. The initial symptoms are generally not specific such as anorexia, irritability, and lethargy. Fever is the most common symptom, estimated at around 60% of patients. Progressive bone marrow failure triggers pallor (anemia), bleeding (thrombocytopenia) and it is prone to infection (neutropenia). Anemia, abnormal leukocytes and differential counts and thrombocytopenia generally occur in the diagnosis, describing the degree of bone marrow replaced by leukemic lymphoblasts. Severe bleeding is rare, although low platelet counts are 20 x 10^9/L, without infection and fever. Coagulopathy is usually mild and can occur in T-ALL and is rarely associated with severe bleeding.[2,7]

Patients with lymphoid malignancies experience Central Nervous System (CNS) disorders more often than patients with myeloid leukemia.[8,9] Intracranial hemorrhage can be an early clinical symptom in patients with blood malignancy.[8,10] A retrospective study of intracranial hemorrhage in patients with blood malignancies getting a higher incidence of intracranial bleeding in AML patients than patients with other blood malignancies.[10] Intracranial bleeding as CNS involvement can also occur due to chemotherapy in ALL patients. Bleeding and thrombosis occurred in children with ALL treated with polychemotherapy include L-Asparaginase (L-Ase).[11,12]

CASE DESCRIPTION

A 13-year-old boy came to the Emergency Room of Sanglah Hospital (1st August 2018) with fever and red spots throughout the body. The fever was appeared since one year ago, came and go. He said the fever appeared when he exhausted after playing soccer. Fever appeared three days ago (Sunday, 29th July 2018), with the highest temperature is 38°C, relieve with paracetamol.

Bruises and red spots were appeared all over the body since four days ago (Saturday, 28th July 2018). Early spots appeared on the chest then spread a lot. There is no itchy, no trauma history, no bleeding gums, and no nosebleeds. He defecated softly three times since yesterday and frequently urinating in yellow. The decrease in body weight was said to have been realized by the patient's parents for one week. Pain in the joints is denied.

The patient had never experienced the same complaint before. The patient was the 4th child of 4 siblings, and in the family, there were no complaints from the patient as well. The patient is currently a junior high school student. The history of the patient's nutrition was said to have 3-month breastfeeding. His natural history of growth and development was consequent according to a growth period. There was no history of allergies.

The physical examination of the patient had the impression of severe pain with a blood pressure of 150/70 mmHg, axillary temperature 37.8°C, 162 cm in height and 45 kg in weight. The patient's consciousness was *compos mentis* arrived with general status appeared pale anemic, there was an enlarged gland in the right and left collar region and inguinal with a size of about 1-2 cm, thoracic within normal limits, palpable 3 cm below the *xiphoid processus* and *arcus costa*, spleen with Schuffner 3, in warm extremities with capillary refill < 2 seconds, and petechiae appeared.

Investigation of patients with complete blood tests was found to be leukocytosis (WBC 72.69; Ne% 0.93; Neu # 0.67; Retic% 1.0 (corrected 0.56); Retic # 31.9), anemia with hemoglobin 8.43. Thrombocytopenia (PLT 24.67). Complete blood results and physiology of patient hemostasis are shown in the Table 1.

Peripheral blood smears examination at 1st August 2018 showed erythrocytes with hypochromic, anisopoikylositosis with Cigar cell, akhantosit cells, target cell, and normoblast. Leukocytes cell showed increased number, increased limfoblast more than 50%, with no vacoulisation cell and granula toxic. Platelets showed decrease cell counts, with no giant platelet and clumping platelet. Conclusion blood smears examination is ALL, suggested for Bone Marrow Aspiration (BMA) examination. Bone marrow aspiration smear (6th August 2018) showed the erythroid system activity, the myeloid system activity, and the megakaryocyte activity decreased.

Table 1 Complete blood test series and physiology of hemostasis

Date	August 1st 2018	August 8th 2018	August 8th 2018	August 18th 2018	Reference Value
WBC	72.69	121.60	88.65	30.77	4.1 -11.0
NE%	0.93	2.84	0.55	0.58	47-80
LY%	89.33	90,59	93,32	96,18	13-40
MO%	7.38	4.52	3.69	2.12	2.0-11.0
EO%	0.15	0.12	0.07	0.02	0,0-5,0
BA%	2.21	1.92	2.37	1.10	0.0-2.0
NE #	0.67	3.46	0.49	0.18	2.50-7.50
LY #	64.93	110.20	82,73	29.60	1.00-4.00
MO #	5.37	5.50	3.27	0.65	0.10-1.20
EO #	0.11	0.15	0.06	0.01	0.00-0.50
BA #	1.61	2.34	2.10	0.34	0,0-0,1
RBC	3.34	3.78	3.62	3.95	4,5-5,9
HGB	8.43	9.78	8.95	10.83	13.5-17.5
HCT	25.61	29.48	28,51	32,56	41,0-53,0
MCV	76.76	77.98	78,73	82.53	80,0-100,0
MCH	25.28	25.88	24.72	27.45	26,0-34,0
MCHC	32.93	33,18	31.40	33.27	31-36
RDW	15,52	14.96	15.47	15,58	11,6-14,8
PLT	24.67	22.73	20,62	23.83	150-440
MPV	11.26	6.42	6.61	9,12	6.80-10.0
% RETIC	1.0				0.61-2.24
#RETIC	31.9				<1500
PPT		16.6			10.8-14.4
INR		1.42			0.9-1.1
APTT		30.0			24-36

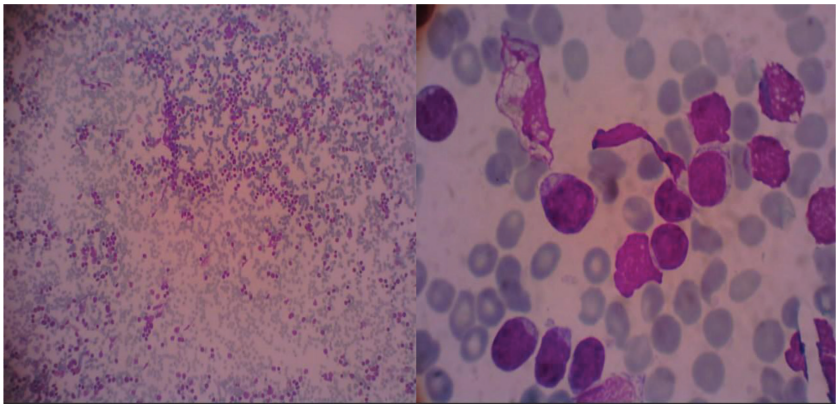

Figure 1 The smear of bone marrow aspiration shows the dominant lymphoblast cell.

It found lymphoblast more than 30% and heterogeneous. It was in accordance with ALL (L2) blast cell dominance result of electrolyte examination within normal limits. .From Imunofenotyping examination was also performed on patients who showed T- ALL cells with aberrant CD 117 expression .

The patient received Dex 5½ saline hydration 2000 ml/m^2 and sodium bicarbonate, allopurinol 10 mg/kg/day. Simple antibiotics are given as much as 2 grams every 8 hours intravenously. Antipyretic paracetamol 500 mg is given every 4 hours if the axillary temperature is> 38° C. The patient gots steroids in the form of dexamethasone 6 mg/m^2 and blood transfusion of 500 ml and chemotherapy will be planned.

During treatment, the patient still had a fever that had disappeared, and on 19/8/2018 the patient has a seizure. One seizure, when the spasms of the hands and feet are said to be stiff and then stomp which lasts approximately 5 minutes. When the patient got seizures, pastient also unconscious. Seizures accompanied by fever with axillary temperature 38.7°C. After the seizure, the patient experienced a decrease of consciousness. The physical examination found a blood pressure of 140/90 mmHg, a pulse rate of 120 times/minute, a respiratory rate of 26 times/minute with a saturation of 97% using an oxygen for 5 liters per minute. The appearance of the right and left palpebral hematoma with the pupil reflex about + / + 3 / 3 mm, no impression of power lateralization was found. At that time, the patient received diazepam 0.2 mg/kg/times giving at a speed of < 2 mg/minute, then given phenytoin 10 mg/kg in 50 cc NS solution, transfusion of 5 TC bags with furosemide premedication. Patients scheduled for a head CT-scan examination in the PICU. It was noted that the planned evacuation of intracranial hemorrhage clot by neurosurgery.

DISCUSSION

This case occurs in children aged 13 years. Leukemia constitutes one-third of cancer cases in children aged 0 to 14 years and 10% of adolescents aged 15-19 years.[1] In Europe, the overall incidence of leukemia in children is around 44 per 1 million people per year between 1988-1997. Lymphoid is found in 81% of cases of leukemia, 15% of acute non-lymphocyte leukemia, CML around 1.5% and non-specific leukemia 1.3% of cases.[13]

In 2016, in Brazil, an estimated 10,070 new cases of leukemia occurred, with prevalence more dominant in men than women.[1,2,7] In France, the incidence of ALL is 1.5 cases per 100,000 people per year and is more common in children aged 4-6 years. The incidence of B-ALL was more frequent than T-ALL.[1,3,9,10] ALL incidents around 1.1/100,000 per year. The peak incidence is in children younger than five years (5.3/100,000 per year), and the incidence decreases as age. Patients over 50 years have an increased incidence and reach a peak at more than 80 years of age (2.3/100,000 per

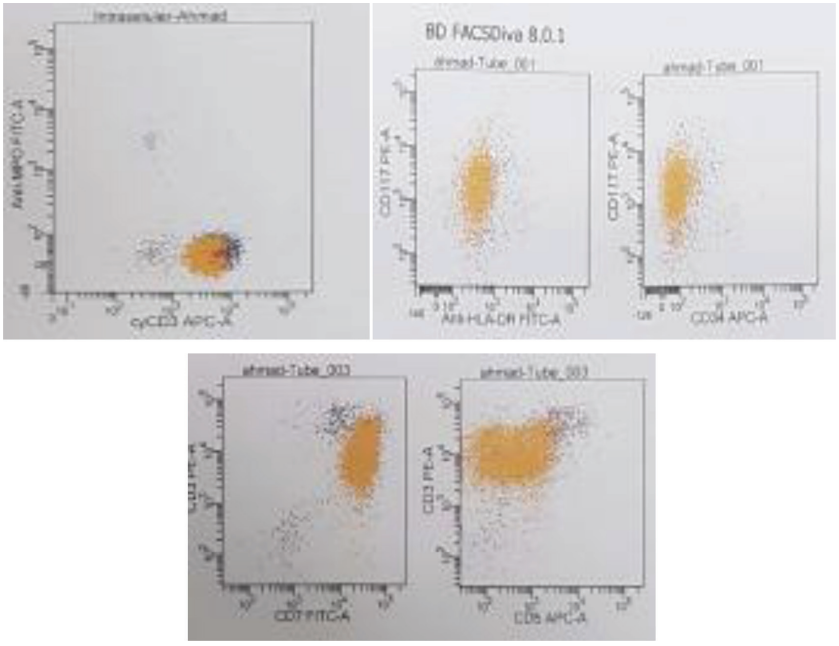

Figure 2 Immunophenotyping impressive T-lineage aberrant CD 117.

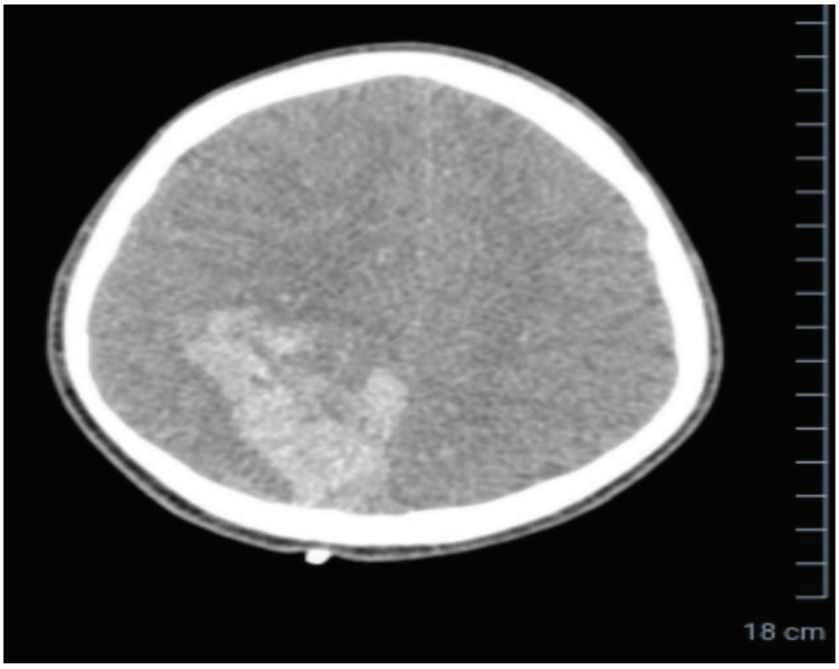

Figure 3 Head CT-scan axial cross section showing an intracerebral hemorrhage with volume + 58 cc with midline shift + 2.6 mm.

year). ALL cases are more dominant in male patients with ratio 1,4 : 1.[14,15]

ALL is described in the presence of immature lymphoid cells in the bone marrow, peripheral blood, and lymphoid organs. Two different malignant cells can be found, namely cell B (B-ALL) and T cell (T-ALL). The incidence of B-ALL was estimated at 80-85% of cases of ALL and T-ALL at 15-20%.[5,15,16]

Complaints that make patients look for treatment is the presence of fever since one year ago, loss of appearance with bruising and reddish spots on the body. ALL symptoms are associated with blast infiltration in the bone marrow, lymphoid system, and extramedular system. Infiltration of blast cells in the bone marrow can cause bone pain and disruption of normal hematopoiesis so that thrombocytopenia and anemia will occur in most patients. Common symptoms of patients with ALL are mainly fever, fatigue, pallor, and weight loss.[13,14,16]

Anemia, leukocytosis, and thrombocytopenia are general descriptions of laboratory parameters during initial enforcement, indicating the degree of bone marrow that has been replaced by leukemic lymphoblasts. The number of leukocytes ranges from 0.1 to 1500 x 10^9/L (median 15 x 10^9/L). Hyperleukocytosis (> 100 x 10^9/L) occurs in 10-15% of patients. Neutropenia (less than 500 granulocytes per mm^3) is a common phenomenon and related to an increased risk of infection. A decrease in platelet count (median 50 x 10^9/L) generally occurs at the beginning of diagnosis and can be distinguished from immune thrombocytopenia, where thrombocytopenia without leukocyte abnormalities is rare in leukemia.

As to enforce leukemia, inspection of bone marrow aspiration smear is essential. Normal bone marrow contains less than 5% blast. Most bone marrow in leukemia is mostly even infiltrated with the leukemic blast. Hypercellular bone marrow specimens and are described as homogeneous cell populations. Leukemia should be suspected in patients with bone marrow containing more than 5% blast. Bone marrow aspiration is difficult to do at the beginning of the diagnosis. Generally, leukemia is classified as ALL when lymphoblast > 25% in bone marrow.[2,8,12] In this case, bone marrow aspiration smear showed lymphoblast > 30%.

The bone marrow morphology examination is the first step in establishing a diagnosis, for primary ALL diagnosis and differentiation from AML. As per ALL's definition, it always involves the bone marrow. Lymphoblast cells have several morphological criteria that can be used to distinguish them from myeloblast. Lymphoblast populations tend to be homogeneous, with varying sizes but generally small in size. Lymphoblasts have a nucleus in the middle, round with a very high ratio of cytoplasmic nuclei to children while adults have a smaller proportion. This cell has diffused chromatin. The nucleolus of lymphoblast cells is not present in small cells — basophilic cytoplasm and sometimes with a single protrusion (hand-mirror cell). Lymphoblast cells have very rare, azurophilic and always negative granules against peroxidase, esterase, and toluidine blue. Given the limitations

of morphological criteria in ALL, examination of flow cytometry analysis is the gold standard for identifying cell lines and a subset of ALL. Based on morphology, there are no criteria that distinguish T-ALL from B-ALL. Besides, it is also complicated to identify B cell lymphoblast from normal B cell lymphoid precursors. [4,9,17]

ALL bone marrow morphology is very varied as mentioned in the FAB (French-American-British) classification working group. ALL accompanied by hypereosinophilia. ALL blast cells are negative against myeloperoxidase (MPO) and other myeloid cytochemical reactions. [4,12,17]

Based on the FAB classification, ALL is divided into L1, L2, and L3 subtypes. The L1 FAB subtype has small lymphoblast features, the nucleus and cytoplasm look uniform with the pale blue cytoplasm, regular nucleus, as well as chromatin are partially condensed with an almost invisible nucleolus and a high nucleocytoplasmic ratio. The L2 FAB subtype has various lymphoblast characteristics, irregular nuclei, very heterogeneous chromatin, weak basophilic cytoplasm and varying nucleocytoplasmic ratio. In the FAB subtype L3 (Burkitt), lymphoblast is very large and contains homogeneous core chromatin, as well as its nucleoli, is dominantly granule.[6,17]

The immunophenotyping examination is a multi-channel flow cytometry (MFC) which is the standard procedure for diagnosis and subclassification of ALL and is also developed as a tool to detect and monitor minimal residual disease (MRD). The European Group's Consensus for Immunological Characterization of Leukaemias (EGIL) states that a 20% threshold is used to determine the positive reaction of blast cells to monoclonal antibodies given. [6,17,18]

Immunophenotyping, the T-ALL cell line, shows T cell markers namely CD1a, CD 2, CD 3 (membranous and cytoplasm), CD 4, CD5, CD 7 and CD 8. CD 2, CD 5, and CD 7 antigens are markers of most Immature T cells, but none of the specific strains were determined.[12,17] In T-ALL, CD 10 expression is quite common (25%) and not specific. The myeloid antigen CD 13 and or CD 33 can also be expressed.[11,12,17] Lymphoblast in T-ALL is TdT+ with the addition of CD3+ cytoplasm, a specific marker for lymphoblastic T-cell abnormalities. In this case, expressed CD 117 which is a myeloid marker on T-ALL, was identified in all subtypes of ALL and maybe as poor predictors. In addition to CD 117, in this section CD 3, CD 7 and CyCD 3 were also positive, when viewed according to the table, this patient diagnosed with Pre T-ALL cell, based on the results of immunophenotyping where T-cell lineage aberrant felt.[5,6]

Before receiving chemotherapy, patients experience seizures caused by spontaneous intracerebral hemorrhage, established based on the results of head CT scan performed on patients, CNS involvement in leukemic patients is clinically very important because of high mortality, but the mechanism of CNS involvement in leukemia is still little known. Leukemia has an indirect effect on the nervous system, causes thrombocytopenia, coagulation factor deficiency, sepsis, complications of chemotherapy and blood vessel wall disordersas reported in the association between high expression of interleukin-15 (IL-15) mRNA in blast ALL and increased risk of CNS involvement.[7,10] Overall, the biological role of IL-15 in CNS leukemia is still unclear. Interleukin-15 has a pleiotropic function by working on various immune cells such as natural killer cells (NK cells). Nk cells are a subset of the lymphocyte innate immune system that plays an important role in cancer immune-surveillance through the ability to recognize and kill cells transforming without prior sensitization. Cytotoxic-mediated NK cells are regulated through a balance of signal transmission of target cell activation and inhibition. IL-15 predominantly regulated development, survival and activation of NK cells. Furthermore, IL-15 showed an increase in NK cytotoxicity to tumor cells by increasing the expression of NKG2D and NK p44 receptors on NK cells and expression of cytotoxic effector molecules. In the previous study, NK cell depletion in mice allowed systemic and CNS involvement in leukemia.[7] The ability to kill human leukemic lymphoblasts by NK cells depends on the expression of the NKG2D receptor. Analysis of bone marrow diagnostic samples of patients with ALL involving the CNS showed very high expression meaning NKG2D and NK p44 receptors. This concludes that the CNS gets immunity protection from the activity of NK cells.[7,15]

Spontaneous intracranial bleeding associated with leukemia can occur at the beginning of the diagnosis or cell treatment. Based of some research on spontaneous intracranial hemorrhage in leukemia, Graus et al. reported incidence of intracerebral hemorrhage in patients with leukemia is only 15%. Pomeranz et al. added that intracranial hemorrhage results from primary thrombocytopenia and infiltration of abnormal leukemia in the central nervous system by 30%. Gmur et al. stated that in the absence of other abnormalities such as coagulation disorders or accompanied by impaired platelet dysfunction, intracranial bleeding is sporadic if the platelet count is above 20 x 10^9/L.[2,7,16] Generally, mild coagulopathy can occur in T-ALL and is rarely associated with severe bleeding.[2,7,16]

Leukocytosis increases the risk of intracranial bleeding. Creutzig et al. reported that infiltration of leukemia cells was found to occur in patients with chronic leukemia blast crisis or acute monocytic leukemia. The aggregation of leukemia cells causes injury to blood vessel endothelial cells, including local circulation, causing bleeding. Acute myeloblastic leukemia causes more intracranial bleeding than acute lymphoblastic leukemia. Larger myeloblast size than lymphoblast causes distribution through small blood vessels is harder and causes increased blood viscosity, leukocytosis, dilation of blood vessels, hypoxia and damage to blood vessels which ultimately lead to bleeding.

Clinical clotting system abnormalities with DIC (disseminated intravascular coagulation) are more common in AML than ALL. These disorders include hypofibrinogen, increased FDP, and prolongation of PT (prothrombin time) and TT (thrombin time). The laboratory parameters will show abnormal results when starting cytotoxic chemotherapy, resulting in complications of severe bleeding.[11,14,15] CD 34 expression in hematopoietic stem cells and also in 60-70% blast cells ALL adult and pediatric patients. The association of CD 34 expression in ALL patients with DIC was reported by Higuchi et al.[4] The white blood cell count of ALL patients was accompanied by higher DIC (reaching 400,000 / µL) compared to patients without DIC. According to Higuchi et al., there were no differences in LDH levels (lactate dehydrogenase), the percentage of blast in the bone marrow, or frequency of lymphadenopathy or hepatomegaly among ALL patients with DIC or without DIC.

CONCLUSION

Case of T- ALL with the coincidence of CD 117 expression in chlidren with intracranial bleeding manifestations before receiving chemotherapy is a rare case, and usually patient with CD 117 expression imunophenotyping having a proggresive and poor prognosis (death).

CONFLICT OF INTEREST

There is no competing interest regarding manuscript.

AUTHOR CONTRIBUTION

All of authors are equally contribute to the manuscript from data extraction, patient's follow up, until data interpretation.

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