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ACQUIRED β−THALASSEMIA IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

(Talasemia-β di Penderita Pengidap Leukemia Limfoblastik Akut (LLA)

Maria Christina Shanty Larasati, Mangihut Rumiris, Mia Ratwita Andarsini, I Dewa Gede Ugrasena, Bambang Permono

ABSTRACT

Thalassemias are heterogeneous group of genetic disorders. β-thalassemia is existed due to impaired production of beta globins chains, which leads to a relative excess of alpha globin chains. The abnormalities of haemoglobin synthesis are usually inherited but may also arise as a secondary manifestation of another disease, most commonly haematological neoplasia. This article presenting two cases of acquired β-thalassemia in children with ALL focusing on the diagnosis and the possible relationship between the two haematological diseases. The first case is a four (4) year old boy with ALL-L1 type at maintenance phase of chemotherapy, he suffered from anaemia with Hb 8.0 g/dL, WBC 22,600/mm^3 and platelets count of 200,000/mm^3, peripheral blood smear revealed anisocytosis, polychromes, hypochromia, basophilic stippling, and normoblastocytes. The result of Hb electrophoresis of Hb A of 54.9%, Hb F of 29.4%, Hb E of 13.4% and Hb A2 of 2.3%. The patient was diagnosed as ALL-L1 type and β-thalassemia. The second case, is a 13 year old girl with remission ALL-L1 type after chemotherapy, she suffered from anaemia with Hb 6.7 g/dL, WBC 12,400/mm^3, platelet count was 200,000/mm^3, and peripheral blood smear obtained anisocytosis, hypochromia, normoblastocytes, myelocytes and basophilic stippling. The result of Hb electrophoresis are: Hb F 0.41%, Hb A1c 0.78%, Hb A2 2.95% with the conclusion of a β-thalassemia trait, this patient was diagnosed with ALL-L1 type remission + β-thalassemia trait. The case reviewers assume that acquired β-thalassemia which happened in those patients were the altered expression of globin chain which mechanism for this syndrome might be the acquisition of a mutation that affects RNA or proteins involved in β-globin gene regulation and resulting the reduction of the (α/β)-globin biosynthetic ratios, or/and associated with chemotherapy-inducement.

Key words: *β-thalassemia, children, acute lymphoblastic leukemia*

ABSTRAK

Talasemia adalah kelompok kelainan genetik pembentukan hemoglobin. Di talasemia-β hasilan rantai β terhambat, sehingga menyebabkan rantai β meningkat. Kelainan pembentukan hemoglobin bersifat diturunkan, tetapi dapat muncul sebagai manifestasi sekunder dari beberapa penyakit, pada umumnya berupa keganasan hematologis. Tujuan laporan dua kasus talasemia-β di penderita LLA ini, menitikberatkan hal terkait tata diagnosis dan kemungkinan hubungan kedua kelainan hematologis tersebut. Kasus pertama ialah seorang anak laki-laki berusia 4 tahun dengan LLA-L1 sedang menjalani kemoterapi tingkat rumatan, penderita mengalami anemia dengan Hb 8,0 g/dL, WBC 22.600/mm^3, platelet 200.000/mm^3, hapusan darah tepi didapatkan anisositosis, polikromasia, hipokromia, basophilic stippling, normoblast. Hasil Hb electrophoresis: Hb A 54,9%, Hb F 29,4%, Hb E 13,4% dan Hb A2 2,3%. Penderita didiagnosis LLA-L1 dan talasemia-β. Kasus kedua, anak perempuan berusia 13 tahun dengan LLA-L1 remisi pasca kemoterapi, penderita mengalami anemia dengan Hb 6,7 g/dL, WBC 12.400/mm^3, platelet 200.000/mm^3, hapusan darah tepi didapatkan anisositosis, hipokromia, normoblast, mielosit, basophilic stippling. Hasil Hb electrophoresis: Hb F 0,41%, Hb A1c 0,78%, Hb A2 2,95%. Penderita didiagnosis LLA-L1 remisi dan talasemia-β trait. Dalam kasus ini dapat didugakan bahwa talasemia-β di penderita LLA terjadi karena perubahan ekspresi rantai globin dengan mekanisme perpindahan RNA atau pengaturan gen β globin yang menyebabkan berkurangnya angka banding biosintesis (α/β)-globin, atau/dan dihubungkan dengan dipicu kemoterapi yang diberikan.

Kata kunci: Talasemia-β, anak-anak, leukemia limfoblastik akut

INTRODUCTION

Thalassemias are heterogeneous group of genetic disorders, characterized by defect on the synthesis of one or complete globins chains. Specifically, β-thalassemia which existed due to the impaired production of beta globin chains, which leads to relative excess of alpha globin chains.[1] The abnormalities of haemoglobin synthesis are usually inherited, but may also arise as secondary manifestation of another

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disease, most commonly haematological neoplasia.[2] Previous studies of acquired Hb H disease in leukemias have documented the profound reduction of (α/β) globin biosynthetic ratios in all patients. Analysis of total bone marrow RNA from two patients has shown (α/β)-globin mRNA ratios of 0.01 and 0.05.[3]

The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) have been done retrospectively reviewed the databases of seven studies on acute lymphoblastic leukaemia (ALL) to identify patients with associated genetic disease, other than Down's syndrome. Forty-two patients (0.62%) were reported to have associated genetic conditions that included β-thalassemia (n=10), ataxia-telangiectasia (n=10), G6PDH deficiency (n=4), neurofibromatosis (n=4), Soto's syndrome (n=2) and other individual conditions.[4,5]

The purpose of this paper is to present two cases of acquired β-thalassemia in children with ALL, focusing on the diagnosis and the possible relationship between the two haematological diseases.

The conclusion was diagnosis of acquired β-thalassemia in ALL has been established based on the peripheral blood smear obtained basophilic stippling and Hb electrophoresis. The reviewers assume that acquired β-thalassemia which happened in their studied cases was an altered expression of globin chain that mechanism for this syndrome might be the acquisition of a mutation that affects RNA or proteins involved in β-globin gene regulation results reduction of the (α/β)-globin biosynthetic ratios, or/and associated with chemotherapy-induced.

THE CASE REPORTS

Case 1

The first case is concerning a 4 year old boy with Acute Lymphoblastic Leukemia (ALL)-L1 type and received chemotherapy of standard risk Indonesian ALL protocol 2006. He showed good response to chemotherapy and follow-up to continue the rest of the related protocol.

On August 18th, 2011 the patient came to the paediatric haematology oncology outpatient clinic to proceed with the maintenance phase of chemotherapy. He had no specific complaints, all physical examination was of within normal limit. Complete blood count examination obtained haemoglobin level of 8.0 g/dL, white blood count of 22,600/mm^3 with no eosinophiles, no basophiles, no band neutrophiles, 37% segmented neutrophiles, 63% lymphocytes, and no monocytes, and platelets count of 200,000/mm^3. The peripheral blood smear revealed anisocytosis, polychromes, hypochromia, basophilic stippling, and normoblastocytes. Hemoglobin electrophoresis was advised to rule out thalassemia.

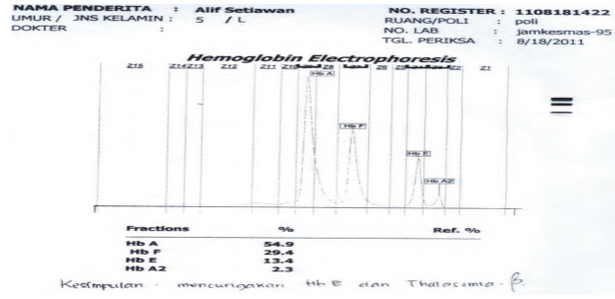

Figure 1. The result of Hb electrophoresis case 1

The haemoglobin electrophoresis performed on August 18th, 2011 with result of Hb A of 54,9%, Hb F of 29.4%, Hb E of 13.4% and Hb A2 of 2.%. The results of the current examination the patient was diagnosed as ALL-L1 type and β-thalassemia.

Case 2

The second case a 13 year old girl was an ALL-L1 type patient post chemotherapy on April 15th, 2009. In December 9th, 2007 a complete blood count showed as followed: haemoglobin level 6.0 g/dL, white blood counts 8,200/mm^3, with 1% eosinophiles, no basophiles, no band neutrophiles, 79% segmented neutrophiles, 20% lymphocytes, and no monocytes, with a peripheral blood smear obtained anisocytosis, polychromes, hypochromia, normoblastocytes and basophilic stippling with platelet count was 200,000/mm^3. From the results of laboratory examinations are recommended for Hb electrophoresis to ensure there any chance of a thalassemia obtained results normal of Haemoglobin A (Hb A 96.5%) and normal Haemoglobin A2 (Hb A2 3.5%) with conclusion normal Hb electrophoresis.

At the end of the treatment (April 15th, 2009) a second bone marrow aspiration revealed normocellular, enough erythropoetic and granulopoetic activity system, enough megakaryocytes, lymphoblast <5%, with the conclusion a remission of ALL.

On July 1st, 2009 she came again for continuing up and complete the blood work examination which showed haemoglobin level of 6.7 g/dL, white blood count of 12,400/mm^3, with 1% eosinophiles, no basophiles, no band neutrophiles, 68% segmented neutrophiles, 31% lymphocytes, no monocytes and platelet count was 200,000/mm^3, with a peripheral blood smear obtained anisocytosis, hypochromia, normoblastocytes, myelocytes and basophilic stippling. Based on the results above she was suspected a relapse of ALL, therefore another bone marrow aspiration performed, resulting in normocellular, enough erythropoetic and granulopoetic system activity, and megakaryocyte with a conclusion of ALL remission, and advised to have haemoglobin electrophoresis. The

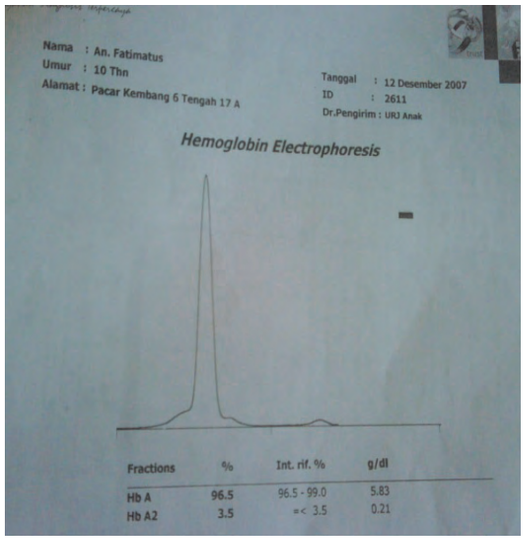

Figure 2. The results of Hb electrophoresis images of the patient of case 2 on December 12th, 2007

result of hemoglobin electrophoresis dated July 3rd, 2009 Hb F 0.41%, Hb A1c 0.78%, Hb A2 2.95% with the conclusion of a β-thalassemia trait. Based on the laboratory results, she was then diagnosed with ALL-L1 type remission+β-thalassemia trait.

DISCUSSION

In the first case, during the treatment of maintenance phase peripheral blood smear revealed basophilic stippling. This condition was unusual in the leukaemia but often found in the haemolytic anaemia and thalassemia. From the results of laboratoric examinations are recommended for Hb electrophoresis to ensure there any chance of a thalassemia obtained results decreased of Haemoglobin A (Hb A 54.9%), increased of Haemoglobin F (Hb F 29.4%) and normal Haemoglobin A2 (Hb A2 2.3%). From the results of the current examination the patient was diagnosed as β-Thalassemia.

In the second case, at the end of treatment from bone marrow aspiration revealed ALL remission. But at the date follow up the 1st July, 2009 from the results of complete blood count revealed anaemia with haemoglobin level 6.7 g/dL, and with a peripheral blood smear obtained anisocytosis, hypochromia, normoblast, myelosit and basophilic stippling. Suspected presence of a relapse process and may be other chance disease advisable to check bone marrow aspiration and haemoglobin electrophoresis obtained results normal Haemoglobin F (Hb F 0.41%) and Hb A2 2.95% with the conclusion of a β-thalassemia trait and the examination of bone marrow aspiration performed showed conclusion ALL remissions. From

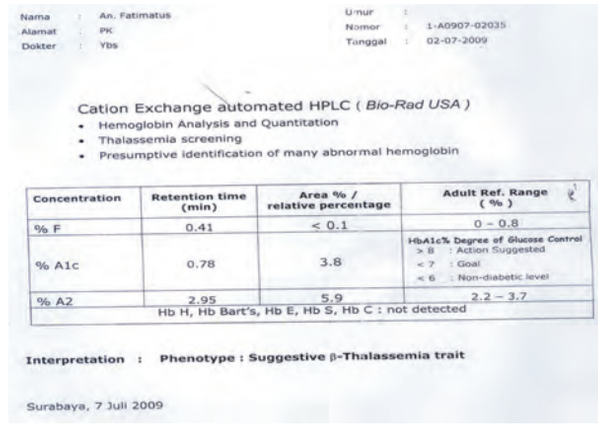

Figure 3. The results of Hb electrophoresis images of the case 2 patient on July 2nd, 2009

the laboratory results on patients was diagnosed as ALL-L1 remission+β Thalassemia trait.

The diagnosis of thalassemia is made also from the founded microcytic hypochromia anaemia, nucleated red blood cells, anisocytosis, poikilocytosis (spiculated tear-drop and elongated cells), basophilic stippling, and nucleated red blood cells on peripheral blood smear.[6.7.8]

In the first case the reviewers get the result of Hb electrophoresis was decreased of Haemoglobin A (Hb A 54.9%), increased of Haemoglobin F (Hb F 29.4%) and normal Haemoglobin A2 (Hb A2 2.3%). From the results of the current examination the patient was diagnosed as β-Thalassemia. And the second case the reviewers found the Hb electrophoresis obtained results normal Haemoglobin F (Hb F 0.41%) and Hb A2 2.95% with the conclusion of a β-thalassemia trait.

Hb electrophoresis is one of the important diagnostic test to know the cause of haemolysis, it helps to identifies the amount and type of haemoglobin present. The following haemoglobin (Hb) types most relevant for diagnosing are HbA, HbF, HbA2. Haemoglobin A (HbA) contain ($\alpha_2 \beta_2$), Haemoglobin F (HbF) contain ($\alpha_2 \gamma_2$), and Haemoglobin A_2 (HbA_2) contain ($\alpha_2 \delta_2$), α chain derived from chromosome 16 and β, γ, δ chains from chromosome 11. HbF is the main oxygen transport protein in the fetus during the last seven months of development in the uterus, these levels decline after six months as adult haemoglobin synthesis is activated while fetal haemoglobin synthesis is deactivated. The HbA takes over soon after as the predominant form of haemoglobin in normal children. Certain genetic abnormalities can cause the switch to adult haemoglobin synthesis to fail, in severe forms of thalassemia, may cause haemoglobin A levels to be low and haemoglobin F levels to be high, however in children less than seven months it could be showing normal result due to the transition from Hb F become Hb A (Figure 4). Normal range for Hb

F based on age shown in (Table 2). Haemoglobin A2 may be increased in β thalassemia or to people who are heterozygous to β thalassemia gene, but it could be normal because the level of Hb A2 increases gradually through the first year of life at which time adult levels are reached.[9,10,11]

A low level of haemoglobin A2 synthesis is physiological in the fetus and neonate. At other stages of life, a low rate of synthesis can be inherited or acquired. Reduced synthesis haemoglobin A2 is relatively common as an acquired disorder as a consequence of iron deficiency or impaired delivery of iron to developing erythroid cells. It should be noted that an acquired condition leading to decreased synthesis of haemoglobin A2 can lower the percentage in a patient with β thalassemia trait and a mild case could obscure the diagnosis. Low haemoglobin A2 percentage, with or without an increase percentage of haemoglobin F may be predictive of leukaemic transformation in aplastic anaemia. Acquired abnormalities leading to an increased or reduced percentage of haemoglobin A2 are summarized in Table 1.[6,12]

β°-thalassemia: a complete absence of globin beta chains and a marked excess of globin alpha chains compared with globin gamma chains. The α/γ ratio is greater than 2.0. β^{+}-thalassemia: a variable degree of reduction of globin beta chains resulting in severe (thalassemia major) to mild (thalassemia intermedia) clinical phenotypes. The imbalance of the α/β and γ ratio is similar to that in β°-thalassemia major.

Although abnormal patterns of haemoglobin synthesis are nearly always inherited, occasionally persons with previously normal haematological function develop aberrant haemoglobin synthesis as an acquired abnormality, usually within the context of haematological malignancy.[2]

Both of the studied cases with ALL developed thalassemia. In the first case thalassemia was diagnosed at one year after treatment of ALL and in the second case was diagnosed after she got remission of ALL. The peripheral blood smear obtained basophilic stippling and the reviewers suspected presence of thalassemia.

Acquired disorder of globin chain synthesis may result from: (i) mutation of a globin gene; (ii) altered methylation status of a globin gene leading to altered expression; or (iii) the influence of other genes on the expression of globin genes. Acquired somatic mutation of globin genes is very rare. Altered expression is much more common.[12]

Table 2. The normal range for Hb F concentration[9]

Age	Hb F concentration (%)
1–30 days	22.8–92.0
1–2 months	7.6–89.8
3–5 months	1.6–42.2
6–8 months	0.0–16.7
9–12 months	0.0–10.5

Alterations in the rates of globin chain synthesis with α: β ratios similar to those observed in thalassemia are quite common in myeloid malignancies. This may be regarded as a mild form of acquired thalassemia. The phenotype of α or β thalassemia is much less common among cases of leukaemia, myelodysplastic syndrome and related disorder than is an alteration in the ratio of α and β globin chain synthesis. When acquired thalassemia occurs the phenotype is most often that of haemoglobin H disease, although acquired α thalassemia trait and β or $\delta\beta$ thalassemia have also been reported.[12]

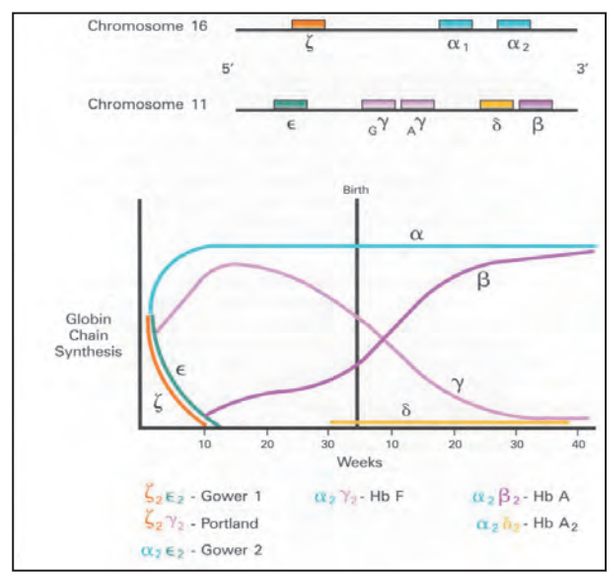

Figure 4. Globin chain synthesis10

Table 1. Hb electrophoresis concentration in Beta-Thalassemia[6]

Haemoglobin Type	Normal	Affected		Carrier
		β-Thal Homozygotes	β^{+}-Thal Homozygotes or β^{+}/β^{o} Compound Heterozygotes	β-Thal Minor
HbA	96–98%	0	10–30%	92–95%
HbF	<1%	95–98%	70–90%	0.5–4%
HbA2	2–3%	2–5%	2–5%	>3.5%

Such perturbations may be of little clinical or haematological consequence, such as when the only change is a minor alteration in the level of fetal haemoglobin (HbF, $\alpha_2\gamma_2$) or the minor adult haemoglobin A2 ($\alpha_2\delta_2$).[13,14] Alternatively, haemoglobin synthesis may become abnormal, as in the rare neoplasm juvenile chronic myelocytes leukaemia (also known as juvenile myelomonocytic leukaemia), in which haemoglobin synthesis often reverts from a normal adult pattern to a fetal pattern.[15,16] In addition to these examples, α- and β-thalassemia have been reported as acquired defects, and the associated abnormal red blood cell production, a consequence of inefficient erythropoietic or haemolysis, may exacerbate the anaemia of the associated haematological malignancy. In 1960, two (2) groups described a series of previously healthy patients with clonally haematopoietic disorders who acquired an unusual form of thalassemia during the course of their illnesses. This syndrome was characterized by marked hypochromia and microcytic anaemia and the presence of HbH, demonstrable by gel electrophoresis and supravital staining of peripheral red blood cells. Patients with similar conditions were soon found to have reduced α-globin-β-globin chain synthesis ratios, demonstrating unequivocally that α-thalassemia could occur as an acquired abnormality in patients with haematological malignancy.[16–19]

Acquired thalassemia is the best characterized of the acquired red blood cell disorders in patients with haematological malignancy, and it is almost always associated with a myelodysplastic syndrome (MDS). At least 2 molecular mechanisms for acquired thalassemia are now recognized: acquired deletion of the globin gene cluster limited to the neoplastic clone and, more commonly, inactivating somatic mutations of the *trans*-acting chromatin-associated factor, which cause dramatic down regulation of globin gene expression.[2]

Minimal criteria for inclusion in the Acquired thalassemia myelodysplastic (ATMDS) registry include 3 components. First, HbH must be demonstrated by electrophoresis, chromatography, or supravital staining (the latter technique is the most sensitive). Second, some form of haematological neoplasia must be present. Finally, given that inherited thalassemia is so common, it is important to exclude any congenital forms of thalassemia predating the haematological neoplasm. Because not all inherited forms of thalassemia are fully characterized, there should be no family history of thalassemia, unless the specific inherited mutation in that pedigree has been defined and carefully excluded in the patient. Using these criteria, it has been possible to construct a profile of this rare group of patients.[2]

In both cases the diagnosis of thalassemia was based on Hb electrophoresis. Form of haematological neoplasia also presented and have been diagnosed as ALL. There was no history of thalassemia in other member family.

It has long been recognized that patients with haematological malignancy and abnormal erythropoiesis may also acquire changes in haemoglobin structure or synthesis, but the molecular basis of such abnormalities remained obscure. However, recent studies of patients with myelodysplastic who acquire thalassemia have identified somatic mutations in a known *trans*-acting regulator of globin gene expression, ATRX (α-thalassemia mental retardation X-linked, named after the phenotype associated with germ line mutations in the gene).[2]

Acquired α-thalassemia (Hb H disease) has been reported in at least 19 patients with a variety of haematological disorders, including erythroleukaemia, sideroblastic anaemia, myelofibrosis, chronic myelogenous leukaemia, acute leukaemia, other less-defined myeloproliferative syndromes, and most recently chronic lymphocytic leukaemia. Since these leukaemia‘s are clonally disorders, the mutation that results in loss of α-globin gene expression may be related to that which leads to the abnormal growth properties of leukaemia cells. Previous studies of acquired Hb H disease in leukaemia‘s have documented a profound reduction of the (a/A)-globin biosynthetic ratios in all patients. Analysis of total bone marrow RNA from two patients has shown (α/β)-globin mRNA ratios of 0.01 and 0.05.[3]

In the reviewers both studied cases, unfortunately they did not performed analysis genetic of total bone marrow aspiration. The ratio of (α/β)-globin mRNA might had to shown reduction of the (α/β)-globin biosynthetic ratios.

Normal erythroid cells contain approximately two times more α2- than α1-globin mRNA, a ratio also found in the small amount of α-globin mRNA present in this patient’s bone marrow cells. This small amount of α-globin mRNA might have been present in the abnormal bone marrow cells or it may have been derived from residual normal haematopoietic cells with complete suppression of each α-globin gene in the preleukaemia cells. What mechanisms might then be invoked to explain decreased expression of all four structurally normal α-globin genes? First, two independent structural mutations on each chromosome 16 might have perturbed expression of the two duplicated α-globin genes on each chromosome. Such mutations could be relatively common in leukaemia bone marrow cells but escape attention if only a single mutation affects the α-globin genes on

one chromosome. The unlikely occurrence of two mutations affecting α-globin gene expression in a given clone of abnormal cells could explain the rarity of the acquired Hb H syndrome.[3]

The reviewers mapping studies suggest that such structural mutations might be defined only by molecular cloning followed by refined restriction endonuclease mapping and DNA sequence analysis. The second general mechanism for this syndrome might be the acquisition of a mutation that affects RNA or proteins involved in α-globin gene regulation. Loss of function of a normal positive regulatory factor or the production of a new suppressive factor might explain the coincident loss of expression of all four α-globin genes on two separate chromosomes. Plasmid-viral recombinant expression vectors and hybrid cell systems might be used to test for the existence of such diffusable regulatory substances in patients with preleukaemia and acquired Hb H disease.[3]

The reviewers can assume that acquired thalassemia which happened in their studied case was an altered expression of globin chain that mechanism for this syndrome might be the acquisition of a mutation that affects RNA or proteins involved in α-globin gene regulation results reduction of the (α/β)-globin biosynthetic ratios, or/and associated with chemotherapy-induced.

CONCLUSION

The diagnosis of acquired β-thalassemia in ALL has been established based on the peripheral blood smear obtained basophilic stippling and Hb electrophoresis that result thalassemia. Acquired thalassemia is the characterized of the acquired red blood cell disorders in patients with haematological malignancy, and it is almost always associated with a myelodysplastic syndrome (MDS). The reviewers assume that acquired β-thalassemia which happened in their studied cases was an altered expression of globin chain that mechanism for this syndrome might be the acquisition of a mutation that affects RNA or proteins involved in α-globin gene regulation results reduction of the (α/α)-globin biosynthetic ratios, or/and associated with chemotherapy-induced.

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