

A 7 YEAR-7-MONTH OLD BOY WITH LEUKEMIC RETINOPATHY

Ni Made Rini Suari¹, Widnyana¹, Putu Budhiastra²

Departments of Child Health¹ and Ophthalmology², Medical School, Udayana University Sanglah Hospital Denpasar

ABSTRACT

Ocular problems in patient with leukemia which are called leukemic retinopathy and subhyaloid hemorrhage is one of its feature. Subhyaloid hemorrhage in children with acute lymphoblastic leukemia (ALL) is rarely happened. We reported a boy 7 year 7 month old, complained sudden blurred vision on his both eyes and diagnosed with acute lymphoblastic leukemia. When patient had complained his vision, result of routine hematology showed anemia, thrombocytopenia, and leukocytosis. Treatment of leukemic retinopathy in this patient was supportive and causal therapy with transfusion of thrombocyte concentrate, hydration for leukocytosis, giving chemotherapy intrathecal methotrexate and systemic (vincristine, daunorubicin, L-asparaginase). We found gradually undergone resolution of subhyaloid hemorrhages, visible flame shaped thin, and his vision recovered nearly completely to 6/6 OD and 6/20 OS. [MEDICINA 2013;44:44-49]

Keywords: children, leukemic retinopathy, acute lymphoblastic leukemia

SEORANG ANAK LAKI USIA 7 TAHUN 7 BULAN DENGAN RETINOPATI LEUKIMIA

Ni Made Rini Suari¹, Widnyana¹, Putu Budhiastra²

Bagian/SMF Ilmu Kesehatan Anak¹ dan Mata² Fakultas Kedokteran Universitas Udayana/Rumah Sakit Umum Pusat Sanglah Denpasar

ABSTRAK

Gangguan penglihatan pada pasien dengan leukemia disebut retinopati leukemia dan salah satu kejadian yang ditemui adalah perdarahan subhyaloid. Perdarahan subhyaloid jarang terjadi pada anak dengan leukemia limfoblastik akut (LLA). Kami melaporkan seorang anak laki usia 7 tahun 7 bulan dengan LLA yang mengalami keluhan penglihatan kabur pada kedua mata. Pada pemeriksaan oftalmoskopi ditemukan adanya perdarahan pada subhyaloid. Ketika keluhan muncul, pasien dalam kondisi anemia, trombositopeni, dan leukositosis sesuai sebagai penyebab terjadinya retinopati leukemia. Tata laksana yang diberikan pada pasien ini adalah suportif dan kausal, yaitu dengan tranfusi trombosit konsentrat, hidrasi pada leukositosis, kemoterapi sistemik, dan kemoterapi intratekal (vincristine, daunorubicin, L-asparaginase). Secara bertahap ditemukan resolusi pada perdarahan suhyaloid, penipisan pada lapisan perdarahan, dan perbaikan visus penglihatan mendekati normal OD 6/6 dan OS 6/20 [MEDICINA 2013;44:44-49]

Kata kunci : anak, retinopati leukemia, leukemia limfoblastik akut

INTRODUCTION

Leukemia is defined as a neoplastic blood disorder characterized by the overproduction of abnormal white blood cells. It can be divided into two types; myelogenous and lymphoblastic. At least 50%

all leukemias manifest some ocular involvement.¹The ocular complications of leukemia may be due to a direct involvement by leukemic infiltrates or secondary to concomitant anemia or thrombocytopenia. Leukemic retinopathy is a common manifestation of leukemia and found

in both acute and chronic forms. Features of leukemic retinopathy include multiple preretinal and intraretinal hemorrhages are most commonly found in the posterior pole. Other features include Roth's spots, cotton wool spots, exudates, retinal venous tortuosity,

perivascular sheathing, and neovascularization are also found.¹

Ocular involvement in leukemia is either due to direct infiltration of the orbit and other tissues (iris, choroid, optic nerve), vascular abnormalities affecting the retina (intraretinal hemorrhages, white central retinal hemorrhages, cotton wool spots, macular hemorrhages, subhyaloid hemorrhages, vitreous hemorrhages), or neuro-ophthalmic signs (papilloedema secondary to raised intracranial pressure, isolated cranial nerve palsies) of central nervous system (CNS) disease.²

In leukemic case, the time appearance of ocular evaluation is not specified. It is possible that the ocular evaluation is performed at any time during the course of illness, only when the patient demonstrated ocular symptoms, or in patient with high risk factors such as central nervous system leukemia, severe thrombocytopenia or marked leucocytosis.^{2,3}

Before the era of effective antileukemic therapy, retinopathy is believed to have no prognostic significance in acute leukemia. However, it is important to consider an ocular evaluation at the time of diagnosis of acute leukemia in adults and children since recent reports have demonstrated that the presence of ocular involvement is associated with poor prognosis in acute childhood leukemias.⁴

We reported a case that demonstrates the appearance of leukemic retinopathy associated with

extensive retinal hemorrhages (subhyaloid hemorrhages) occurring in the absence of trauma in a patient with ALL. We reported the clinical features, relevant literature, and suggested mechanisms for subhyaloid hemorrhages in such a situation.

CASE REPORT

A 7 year 7 month old boy who was born and lived in Mengwi, was referred from Kapal Hospital with suspected leukemia. He came to Kapal Hospital with chief complaints fever, pale, and distended abdomen. He suffered from fever 3 weeks before hospitalized. Fever without coughing, diarrhea, dyspnea, dysuria, and convulsion. Other symptom was pale since 2 weeks before hospitalized, started from eyelids and lips and spread on his hands and feet. There were no history of bleeding on skin and gum nor redness urine or blackish stool.

When treated at RSUD Kapal on September 22nd, 2011, he had undergone routine hematology and blood smear evaluation. Result of routine hematology was leukocyte $41.6 \times 10^3/\mu\text{L}$ (neutrophil 4.79, lymphocyte 34.7, monocyte 1.72) $10^3/\mu\text{L}$, hemoglobine 8.71 g/dL, hematocrite 25.8%, MCV 70.6 fl, MCH 23.8 pg, MCHC 33.80 g/dL, RDW 14.70, platelets 21.7 k/uL, and blood smear result was suspicious for ALL.

On September 26th 2011, he came again to Kapal Hospital with severe pale, fever, and pain of his leg. When he arrived at Kapal Hospital, his doctor

gave advice to go to Sanglah Hospital in order to do follow through examination.

Blood examination was taken when he went to Sanglah Hospital, and showed similar results, high WBC count with lymphocyte predominance, normochromic normocytic anemia with low platelet count (leukocyte 60.20 k/ μL , neutrophil 4.14 k/ μL , lymphocyte 50.32 k/ μL , monocyte 4.14 k/ μL , hemoglobine 5.77 g/dL, hematocrite 17.78, MCV 68.40 fl, MCH 23.11 pg, MCHC 33.79 g/dL, RDW 14.06, platelets 20 k/uL. Blood smear was evaluated and showed erythrocyte normochromic, anisocytosis, normoblast, leukocyte increase, homogenous lymphoblast predominance, decrease of platelets, and was concluded with suspicion ALL (L1). At Sanglah hospital patient was later undergone bone marrow aspiration (BMA) to confirm the diagnosis. Therapy applied was hydration for leukocytosis, transfusion of packed red cell (PRC), transfusion of platelets, and nutritional therapy.

After 12 days of treatment, he had no fever and having better appetite and bone marrow was done. Laboratory result showed leukocyte 67.40 k/ μL neutrophil 3.49 k/ μL , lymphocyte 58.63 k/ μL , monocyte 3.34 k/ μL , hemoglobine 8.1 g/dL, hematocrite 22.48%, MCV 73.49 fl, MCH 26.52 pg, MCHC 36.09 g/dL, RDW 17.66, platelets 24.29 k/uL. Result of bone marrow aspiration was hypercellularity, erythroid system decreased activity, myeloid system decreased

activity, megakaryocyte system decreased activity, other cell showed >50% infiltration of lymphoblast with homogen morphology small size, and conclusion appropriate ALL (L1).

On-day 19 (October 15th, 2011) he started to has blurred vision and flare sensation on both eyes. There was no ocular or head trauma, no history of blackish stool, nose bleeds nor easy bruising. In that time, routine hematology was leukocyte 139.50 k/ μ L, neutrophil 2.69 k/ μ L, lymphocyte 116.40 k/ μ L, monocyte 0.41 k/ μ L, hemoglobin 6,30 g/dL (MCV 77,0 fl, MCH 28,40 pg, MCHC 36,80 g/dL), hematocrite 17.10%, RDW 18.10, platelets 11 k/ μ L, LUC 14.30%.

Patient then consulted to Ophthalmology Department and examination was done at the bedside secondary to patient's weakness and nausea. Visual acuity was 5/60 oculi dextra (OD) and 3/60 oculi sinistra (OS), pupils were 4 mm and reactive, with no evidence of a relative afferent papillary defect. Anterior segment examination was grossly normal. Conclusion from ophthalmologist was leukemic retinopathy on both eyes and later examined with funduscopy.

On-day 23 of treatment (October 19th, 2011) funduscopy was done and showed anterior segment ODS were normal. Posterior segment OD showed pale retina, subhyaloid hemorrhages in inferior macula with Roth spots at inferonasal quadrant, flame shaped at

superotemporal, and superior quadrant. Posterior segment OS showed pale retina, subhyaloid hemorrhages in inferior macula, and flame shaped at

ODS was normal. Posterior segment OD showed volume of hemorrhages of subhyaloid was decreased without Roth spots and thin flame shaped.



Ocular dextra



Ocular sinistra

Figure 1. Funduscopy examination at October 19th 2011, showed manifestation hemorrhages was flame shaped with fluid level.

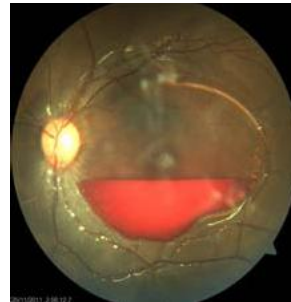


Figure 2. Funduscopy at November 17th 2011.

superotemporal (**Figure 1**).

Acute lymphoblastic leukemia treatment started from October 22nd 2011 using high risk 2006 protocol. On October 26th 2011, methotrexate intrathecal was administered, accompanied with liquor cerebrospinalis (LCS) analysis to examine whether blast cell invade CNS. Liquor cerebrospinalis analysis was performed to differentiate blurring vision from blast invasion to CNS especially optic nerves. Result from LCS analysis found no blast cell.

On November 17th 2011, we made second evaluation for blurring vision. Ophthalmologist found VA OD 6/30 OS 6/60, anterior segment

Posterior segment OS showed decreased of volume subhyaloid hemorrhages (**Figure 2**).

Third evaluation that made on November 25th 2011 found improvement on vision capability with VA 6/12 and 6/30 (**Figure 3**). Ophthalmologist evaluation on December 22nd 2011 found no blurring vision with VA 6/6, anterior segment was normal, and posterior segment showed subhyaloid hemorrhages with improvement. On left eye we found visus 6/20 with normal anterior segment and improvement of subhyaloid hemorrhages on posterior segment (**Figure 4**). Until December, patient had 6 times

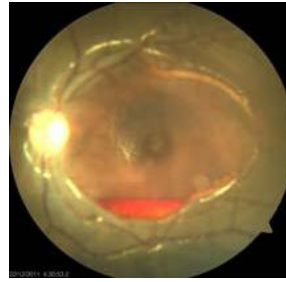


Figure 3. Funduscopy at November 25th 2011.



Figure 4. Funduscopy at December 22nd 2011.

chemotherapy L-Asp 6000 μ /m², 5 times of Daunorubicin 30 mg/m², 7 times of vincristine 1,5 mg/m², and 4 times of methotrexate intrathecal. Routine hematology was done and showed leukocyte 2.27 k/ μ l, neutrophil 35.4 k/ μ L, lymphocyte 49,98 k/ μ L, hemoglobin 10.6 g/dL (MCV 83.10; MCHC 37.90), hematocrite 32.10%, platelets 501 k/ μ L.

DISCUSSION

Leukemia is an abnormal proliferation of one or more cell lines in the blood at the expense of the normal cell lines. Differentiation of leukemic type is determined by the line of hematopoiesis (lymphoblastic versus myelocytic) and the rate of progression (acute versus chronic), with acute leukemias making up the majority in those under 20 years of age. Acute lymphoblastic leukemia (ALL) accounts for approxi-

mately 80% of acute leukemias, which acute myeloid leukemia (AML) responsible for the remaining 20%.⁵

The retina is involved in leukemia more often than any other ocular tissue. The early manifestations (because of hematological disturbance) are venous dilatation and tortuosity. Hemorrhages may occur in all levels of the retina, usually in the posterior pole, and may extend into the vitreous.⁶

Ocular involvement in leukemia is either due to direct infiltration of the orbit and other tissue (iris, choroid, optic nerve), or vascular abnormalities affecting the retina (intra-retinal hemorrhages, white centered retinal hemorrhages, cotton wool spots, macular hemorrhages, subhyaloid hemorrhages, vitreous hemorrhages), or neuro ophthalmic signs (papilloedema secondary to raised intracranial pressure, isolated cranial nerve palsies)

of CNS disease.^{6,7} In our case, patient was a boy aged 7 year 7 month old and diagnosed with ALL according to the clinical vignette-based as well as histopathologic feature. He had suddenly blurred vision.

Leukemic retinopathy is most often manifestation used to denote the ocular manifestation of anemia, thrombocytopenia and increased blood viscosity seen in patients with leukemia. Prevalence of leukemic retinopathy was 49%.⁸ It has been suggested that leukemic infiltration of the ocular is related to high leukocyte counts and that ocular hemorrhages are associated to anemia and/or thrombocytopenia.^{9,10}

Ocular hemorrhages are the most striking feature of leukemia. They tend to occur most commonly at the posterior pole, may be at any level of the retina and may extend into the subretinal or vitreous spaces.¹⁰ Retinal hemorrhages have been described as dot and blot, or flame-shaped, or, classically, as white-centered hemorrhages (Roth's Spot). It has been proposed that these white centred hemorrhages represent an accumulation of leukemic cells, or platelet fibrin aggregates.^{9,10}

The role of anemia in the case of retinal hemorrhages had focused by several authors. The critical blood levels below which retinal hemorrhages may occur are stated to be a hemoglobin concentration of 40 percent and an erythrocyte count of 1,500,000/mm. Severe anemia may result in hypoxia. This is a potent stimulus to the dilatation of retinal veins. Such venous dilatation contributes to

capillary engorgement and increased fragility, thus, the stage is set for easy bleeding. Capillary fragility may be further increased by thrombocytopenia, hypoxia or by bacterial toxins, and those combination of several factors which may produce retinal hemorrhages, and it is quite difficult to evaluate the individual role of any one of the formed elements of the blood.¹⁰

In our case, we found when patient had complained his vision, result of routine hematology showed anemia, thrombocytopenia, and leukocytosis. That time, patient confirmed with ALL (L1). Funduscopic showed there was bleeding flame shaped with Roth spots as well as subhyaloid hemorrhages in inferior macular on right eye. On the left eye seen any hemorrhages flame shaped and subhyaloid hemorrhage more spacious if compared to the right eye. This picture was likely caused by anemia and/or thrombocytopenia.

Hyperviscosity condition can cause venous occlusion characterized by the formation of microaneurysma, hemorrhages of the retina, and neovascularisation. Blockage of vein leads to hypoxia of retinal tissue layer and nerve fibers of the retina that shows as cotton wool spots.¹⁰ **In our case**, subhyaloid hemorrhage can cause of hyperviscosity of blood other than thrombocytopenia condition with level of leukocyte 139 k/ μ L (leukocytosis).

The funduscopic appearance of preretinal blood depends on its age and the size and shape of the blood filled space. Fresh preretinal blood usually

look like a flame shaped, semilunar, crescentic, or geographic accumulation of dark red blood overlying and obscuring its source. Within time the same accumulation of blood can showed semilunar or crescentic in shape, with a fluid level caused by gravitational settling of the formed elements.¹⁰

Flame shaped hemorrhages are bright red, and lozenge shaped with a striated or serrated outline on at least one margin, and they follow the course of the retinal nerve fibre layer. They occur in the posterior pole of the fundus and are associated with disorders of the superficial radial peripapillary capillaries.¹⁰

Various modalities of treatment for subhyaloid hemorrhage are available including pars plana vitrectomy and pneumatic displacement by intravitreal use of gas and tissue plasminogen, Nd: YAG or green argon laser posterior hyaloidotomy is safe and easy alternative for releasing the entrapped subhyaloid blood into the vitreous and by this way absorption of blood cells in facilitated. The need for unnecessary general anaesthesia in already compromised leukemic children and vitrectomy and its complications are avoided.⁷

Vitrectomy in children is an alternative treatment for subhyaloid hemorrhage but general anaesthesia in already compromised. Child is risky and may be associated with numerous complications; cataract, intraoperative retinal breaks and proliferative vitreoretinopathy. Perforate

the posterior hyaloid face or internal limiting membrane by use of pulsed Nd: YAG laser has been described as a practical substitution to vitrectomy. The only drawback particularly in children is lack of cooperation.⁷ In comparison to vitrectomy, the laser procedure is the ambulatory and painless procedure. The Nd: YAG laser hyaloidotomy will not affect the outcome of deferred vitrectomy. **In our case**, we did not performed vitrectomy and posterior Nd: YAG laser hyaloidotomy. We have known that subhyaloid hemorrhages happened due to ALL. The precise management was intrathecal and systemic chemotherapy. Ophthalmologist decided to observed the VA and frequently funduscopic examination. If, there is no development of visual acuity and resorption of hemorrhage for 6 weeks, they will be undergone intervention.

Leukemic retinopathy is usually not treated directly. Systemic treatment involves the use of chemotherapy, immunotherapy, and radiotherapy. Intraocular leukemic infiltrate is best treated with chemotherapy that is appropriate for the type and stage of leukemia.¹⁰ Supportive therapy with transfusions, antibiotics, and hematopoietic growth factors are also important. Although there is no systematic treatment protocol for cases of ocular leukemic infiltration, many oncologists and ophthalmologists support orbital irradiation as a necessary component of treatment for the

best chance of cure.¹⁰ This is because the eye is thought to be part of the central nervous system, which is often resistant to systemic chemotherapy. The central nervous system is considered a pharmacologic sanctuary for leukemic cells, and prophylactic irradiation with or without intrathecal chemotherapy is given in many cases.⁷ **In our case**, after being given chemotherapy intrathecal methotrexate and systemic (vincristine, daunorubicin, L-asparaginase) gradually undergone resolution of subhyaloid hemorrhages, visible flame shaped thin. His vision recovered nearly completely to 6/6 OD and 6/20 OS.

Ridgway (quoted from¹⁰) reported that 80% of children with acute leukemia died within 10 months following ocular complications. Some literature found a significant ($P < 0.05$) decrease in the 5-year survival rate (21.4% versus 45.7%) in children with acute leukemia and ocular involvement compared to those without ocular disease.³ They reported that 96.4% of children with acute leukemia died within 28 months from the onset of ocular manifestation.¹⁰ **In our case**, prognosis patient is unknown because his treatment for ALL it is still in progress. The presence of ocular involvement in children with ALL is usually a poor prognostic indicator

SUMMARY

IPA 7 year 7 month old boy from Mengwi with chief complaint fever, pale, and

distended of his abdomen. He diagnosed with ALL (L1) since October 8th 2011 with bone marrow aspiration. At October 15th 2011 he had blurred vision and flare. He got examination from ophthalmologist. Result of ocular examination, visual acuity was 5/60 OD and 3/60 OS, pupils were 4 mm and reactive. Conclusion from ophthalmologist was leukemic retinopathy on both eyes and later examination with funduscopy. ALL treatment started from October 22nd 2011 using high risk 2006 protocol. After treated with 6 time L-Asp 6000 μm^2 , 5 time of Daunorubicin 30 mg/m^2 , 7 times of vincristine 1,5 mg/m^2 , and 4 time of methothrexate intrathecal until December 2011 and funduscopy examination evaluation was done showed gradually occurring resolution of subhyaloid hemorrhages and visible flame shaped thin. His vision recovered nearly completely to 6/6 OD and 6/20 OS.

REFERENCES

1. Conter V, Rizzari C, Sala A, Chiesa R, Ci M, Biondi A. Acute lymphoblastic leukemia. *Orphanet Encyclopedia*. 2004;14:1-13.
2. Sharma T, Grewal J, Gupta S, Murray P. Ophthalmic manifestations of acute leukaemias : The ophthalmologist's role. *Eye*. 2004;18:663-72.
3. Levin AV. Retinal hemorrhages: Advances in understanding. *Pediatr Clin N Am*. 2009;56:333-44.
4. Schmidt D. The mystery of cotton-wool spots a review of recent and historical descriptions. *Eur J Med Res*. 2008;13:231-66.
5. Parija S, Roy AK, editors. Ocular manifestations of acute leukemia in childhood – A prospective study. *Proceeding of the 12th MEACO International Congress; 2012 16-20 February; Abu Dhabi. United Arab Emirates: WOC; 2012.*
6. Park SW, Seo MS. Subhyaloid hemorrhage treated with SF6 gas injection. *Ophthalmic surg lasers imaging*. 2004;35:335-7.
7. Rennie CA, Newman DK, Snead MP, Flanagan DW. Nd:YAG laser treatment for premacular subhyaloid hemorrhage. *Eye*. 2001;15:519-24.
8. Tonotsuka T, Imai M, Saito K, Iijima H. Visual prognosis for symptomatic retinal arterial macroaneurysm. *Japan J Ophthalmol*. 2003;47:498-502.
9. Durukan Ah, Kerimoglu H, Erdurman C, Demirel A, Karagul S. Long-term results of Nd:Yag laser treatment for premacular subhyaloid hemorrhage owing to valsalva retinopathy. *Eye*. 2008;22:214-8.
10. Reddy SC, Jackson N, Menon BS. Ocular involvement in leukemia – A study of 288 cases. *Ophthalmologica*. 2003;217:441-5.