A PATIENT WITH CHRONIC MYELOID LEUKEMIA WITH MANIFESTATIONS OF LEUKOSTASIS RETINOPATHY

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Leukostasis retinopathy is a rare eye complication in chronic myeloid leukemia (CML) patients due to hyperleukocytosis. This report discusses the case of a 20-year-old man who was diagnosed with accelerated phase CML and presented with leukostasis retinopathy with symptoms of blurred vision and diplopia. Funduscopic examination revealed retinal hemorrhage, vascular tortuosity, and venous dilatation, which is typical of leukostasis retinopathy secondary to hyperleukocytosis. Supportive therapy was provided in the form of rehydration, correction of hyperuricemia and hyperkalemia, as well as cytoreductive agents imatinib and hydroxyurea, which resulted in significant clinical improvement. This report highlights the importance of early diagnosis and aggressive treatment of leukostasis retinopathy to prevent serious complications.

INTRODUCTION

Leukostasis retinopathy is an eye complication that is still rare in cases of CML (*Chronic Myeloid Leukemia*). A systematic review study conducted by Yassin et al (2022) shows that from 1971 to 2020 there were only 40 cases. Leukostasis retinopathy in CML, which is reported to be 3%, occurs primarily due to infiltration of malignant cells and more often occurs secondarily due to hematological disorders such as anemia and thrombocytopenia as well as hyperviscosity of all blood components (Bintoro, 2019).

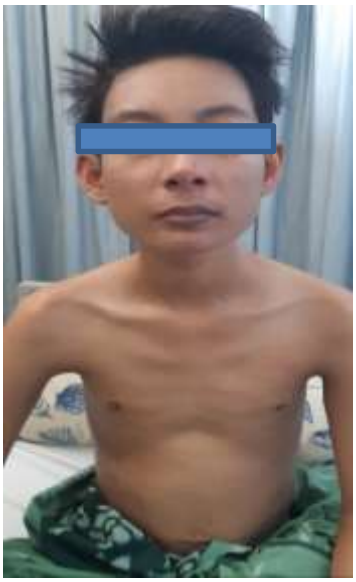
Typical complaints related to leukostasis retinopathy are blurred vision, diplopia, restricted visual field, and the sensation of seeing floating spots (Bintoro, 2019). Clinical manifestations of leukostasis retinopathy that appear on fundoscopy due to direct neoplastic cell infiltration include spots. *roth,* edematous optic nerve, and perivascular sheath. Meanwhile, manifestations due to secondary effects of hyperleukocytosis include retinal hemorrhage (*dot-shaped*, *flame-shaped*, intraretinal, subretinal, and subhyaloid), retinal vein tortuosity, retinal vein obstruction, fine cotton wool spots (*cotton-wool spot*), neovascularization and peripheral microaneurysms, detachment of retinal layers (*serous retinal detachment*) (Bintoro, 2019).

Apart from causing aneurysms and neovascularization, further complications in leukostasis retinopathy cause occlusion of the retinal veins and stasis in all veins. This condition is associated with permanent visual loss and thromboembolic events. According to a

cohort study conducted by Onkoshi and Tsiaras (1992) CML patients without eye complications had a 5 year life expectancy twice as high as CML patients with eye complications (Szeto *et al.*, 2021). Early detection of eye complications in CML is crucial, but research shows that only 5% -10% have eye symptoms detected at the time of initial diagnosis (Bintoro, 2019). Therefore, clinicians need to know and understand the clinical picture and management of leukostasis retinopathy in CML patients. In this article, we report a case of a CML patient presenting with leukostasis retinopathy.

CASE REPORT

A 20-year-old man with, a private job, unmarried came to the oncology clinic at RSU Dr. Soetomo complained of weakness 1 month before entering the hospital and worsening vision loss 2 weeks before entering the hospital. Complaints that the eyes feel blurry and the objects seen are double. Red eyes or watery eyes and frequent eye discharge are denied. The patient also complained that the stomach felt hard and enlarged, often short of breath when walking more than 10 meters. The patient still sleeps with 1 pillow. Apart from that, patients often complain of fever, headaches, cramps in both calves and sometimes ringing in both ears. Coughing, nausea, vomiting, convulsions, and half-body paralysis are denied. There are no complaints about defecation and urination.



The patient was diagnosed with CML in 2018, control was carried out until 2020. In the last 1 year the patient was not controlled. During postal treatment, the patient only remembered to take the drug imatinib, the patient forgot about other drugs.

The patient came with a weak condition, composed of consciousness. Blood pressure 92/56, pulse 105x/minute, respiratory rate 22x/minute, axillary temperature 38◦c, and oxygen saturation 97% with nasal 3 liters/minute. On examination of the head and neck, we found that he appeared anemic and short of breath but did not appear to have cyanosis or jaundice. The eyes do not appear prominent, there is no hyperemia in either eye. Pupil round isochore 3mm/3mm, visual acuity ODS5/20, double vision ODS+/+ On examination of the chest cavity we found that the lungs and heart were within normal limits. On abdominal examination, we

found Schufner's spleen 4. On examination of the extremities, we found warm dry red acral, normal motor strength, and no edema.

The first laboratory examination was obtained **Hb 5.9 g/dl**, Hct 13.5%, MCV 84.4 fl, MCH 36.6 pg, **WBC 614.264 /µL**, Neut 82.3%, Lymph 4.1 %, PLT 156.000/µL, BUN 18 mg/dl, **SK 1.6 mg/dl**, Albumin 4 mg/dl, GDA 125 mg/dl, SGOT 43 U/L, SGPT 33 U/L, **Uric acid 8.8mg/dL, Natrium 148 mg/dl, Kalium 6.6 mg/dl**, **Chloride 110 mg/dl**, Fosfat 3.5mg/dl, **Kalsium 8.3 mg/dl**, PPT 11.5 seconds, **APTT 48.6 seconds**, Non-reactive HBsAg, Non-reactive Anti-HCV, Non-reactive Rapid HIV, Non-reactive SARS cov-2 PCR Swab, Blood Gas Analysis: pH 7.45, pCO2 25, pO2 114, HCO3 17.4, BEecf -6.6, SO2 97% *nasal 3 liters/minute*. with a PF ratio of 380. Complete urine examination: albumin: creatin >=300, specific gravity 1.07, negative bilirubin, negative erythrocytes, negative glucose, clarity *clear*, ketone negative, leukocyte negative, nitrate negative, protein *trace*. Examination of the peripheral blood smear shows: normochromic normocytic anemia, anisopoikilocytosis, leukocytosis with 14% myeloblasts, suspicious for accelerated phase CML.

On examination of the thorax, we found cardiomegaly with a CTR of 58% and there were no abnormalities in the lung. On ODS funduscopic examination: ODS fundus reflex was positive, second nerve papillae had blurry boundaries in all quadrants, the color of the sligt was hyperemic, peripapillary ODS was positive for bleeding, ODS roth spots and exudates were not found, flame-shaped ODS bleeding was found in 4 quadrants, vascular tortuosity was found in ODS, and dilated veins. The conclusion from fellow ophthalmologists was that the picture resembled ODS *leukemic retinopathy* and patients are treated together.

Based on the data above, we diagnosed the patient with accelerated phase CML (BCR ABL detected), normocytic normochromic anemia (5.9), leukostasis retinopathy, hyperkalemia (6.6 mg/dl), hyperuricemia (8.8 mg/dl), BATTERY. Our patient planned rehydration therapy inf Nacl 0.9% 1000 cc in 1 hour, then infusion Nacl 0.9% 1000cc /24 hours drinking a maximum of 1000 cc/24 hours, PRC transfusion 2 calf/day until hb > 10g/dl, correction of hyperkalemia and hypocalcemia calcium gluconate 1 ampoule of slow bolus and D40 and 2 units of insulin are given 2 times 30 minutes apart, in addition, imatinib 0-0-4, hydrea 0-0-4, allopurinol 1x300 mg, and paracetamol 500 mg if fever. The patient is currently contraindicated for leukapheresis because the hemodynamic condition is unstable, and there is prolongation of hemostasis function.

DISEASE TRAVEL

On the 2nd day of treatment, the patient still felt blurry vision, was no longer as weak as yesterday, there was no fever, shortness of breath, ringing in the ears and cramps. The patient is in moderate condition, compos mentis consciousness. Blood pressure 100/68 pulse 100x/minute, respiratory rate 20x/minute, axillary temperature 36.7◦c, and oxygen saturation 95-96% without supplemental oxygen. Input 2500 cc, output 3250 cc, balance -250 cc. Laboratory tests show results Natrium 145 mg/dl, Kalium 4.7 mg/dl, Klorida 100 mg/dl, Fosfat 4mg/dl, Kalsium 9 mg/dl.

On day 3 of treatment, the patient's vision is starting to clear, but there is still double vision, he is no longer as weak as yesterday, there is no fever, shortness of breath, ringing in the ears and cramps. Input 2000 cc, output 3750 cc, balance -750 cc. The patient is in moderate condition, compos mentis consciousness. Blood pressure 105/60, pulse 98x/minute, respiratory

rate 20x/minute, axillary temperature 36.7˚c, and oxygen saturation of 97% without supplemental oxygen. ODS Vision 6/20. Hb 9.3 g/dl, Hct 13.5%, MCV 84.4 fl, MCH 36.6 pg, **WBC 553.067 /µL**, Neut 81%, Lymph 3.7 %, PLT 149.000/µL, BUN 9 mg/dl, SK 0.7 mg/dl, Albumin 4 mg/dl, Asam urat 4.2mg/dL.

On day 5 of treatment, the patient's vision began to clear, there was no double vision, he was no longer as weak as yesterday, and there was no fever, shortness of breath, ringing in the ears and cramps. Input 2500 cc, output 3000 cc, balance 0. The patient is in moderate condition, compos mentis consciousness. Blood pressure 105/60, pulse 98x/minute, respiratory rate 20x/minute, axillary temperature 36.7˚c, and oxygen saturation of 97% without supplemental oxygen. ODS Vision 6/20**. Hb 8.5 g/dl,** Hct 23.6%, MCV 84.3 fl, MCH 30.4 pg, **WBC 509.041 /µL**, Neut 81%, Lymph 3.7 %, **PLT 117.000/µL**, BUN 14 mg/dl, SK 0.6 mg/dl, Albumin 3.5 mg/dl, Uric acid 3.6mg/dL, Sodium 145 mg/dl, Potassium 4.3 mg/dl, Chloride 107 mg/dl, Phosphate 4mg/dl, Calcium 8.5 mg/dl, SGOT 35U/L, SGPT 17 U/L. We postponed the administration of hydrea because there was a decrease in hb and platelets, the patient was only given imatinib 0-0-4 and another PRC transfusion of 2 kolf/day hb up to 10g/dl.

On the 10th day of treatment, the patient has no complaints. Input 2000 cc, output 2750 cc, balance -250cc. The patient is in sufficient condition, compos mentis consciousness. Blood pressure 105/60, pulse 98x/minute, respiratory rate 20x/minute, axillary temperature 36.7˚c, and oxygen saturation of 97% without supplemental oxygen. ODS Vision 6/20**.** Hb 10 g/dl**,** Hct 23.6%, MCV 84.3 fl, MCH 30.4 pg, **WBC 393.00 /µL**, Neut 81%, Lymph 3.7 %, **PLT 130.000/µL**, BUN 19 mg/dl, SK 0.9 mg/dl, Albumin 3.5 mg/dl, Uric acid 3.6mg/dL, Sodium 145 mg/dl, Potassium 4.3 mg/dl, Chloride 98 mg/dl, Phosphate 4mg/dl, Calcium 8.9 mg/dl. Our patient is planning outpatient care.

When the patient was outpatient, on October 18 2021, the patient had no complaints. The laboratory showed Hb 9.6 g/dl**,** Hct 30%, MCV 80.9 fl, MCH 25.5 pg, WBC 229,000 /µL, Neut 81%, Lymph 3.7 %, PLT 210,000/µL, BUN 19 mg/dl, SK 0.4 mg/dl, Albumin 3.5 mg/dl, Uric acid 7 mg/dL, Sodium 145 mg/dl, Potassium 4.7 mg/dl, Chloride 98 mg/dl, Phosphate 4mg/dl, Calcium 8.9 mg/dl, SGOT 32 U/L, SGPT 29 U/L. During control at the eye clinic, the patient had no complaints of blurred or double vision, sharp eye vision was 6/6. Funduscopic examination was not obtained *roth spot* or bleeding in 4 quadrants.

laboratory on March 28 2022 showed Hb 11 g/dl**,** Hct 34%, MCV 69 fl, MCH 22.5 pg, WBC 5083 /µL, Neut 81%, Lymph 3.7 %, PLT 100.000/µL, Asam urat 5.7 mg /dL, Natrium 146 mg/dl, Kalium 4 mg/dl, Klorida 100 mg/dl, Kalsium 8.6 mg/dl.

DISCUSSION

The pathophysiology of leukostasis retinopathy can occur in two ways, namely direct neoplastic cell infiltration into the vitreous organ through neovascularization of the optic disc and vitreous hemorrhage. Apart from that, it can be secondary, namely the effects of

hyperleukocytosis (Vicini *et al.*, 2021). Hyperleukocytosis and a decrease in the deformability of blood cells cause hyperviscosity. This hyperviscosity causes stagnation and decreased blood flow which results in torn capillaries and the formation of microaneurysms (Gupta *et al.*, 2021). This process also underlies the rare incidence of leukostasis retinopathy in cases of chronic leukemia compared to acute leukemia because the white blood cell components in this phase are more able to deform than young cells (*blahs cell*) so that hyperviscosity and stagnant processes do not occur (Vicini *et al.*, 2021).

In this case, based on the results of the peripheral blood smear, the patient experienced an accelerated phase of CML where in this phase the young cells increased by more than the same as 15% -29%, making it possible for the patient to experience retinopathy leukostasis.

Typical complaints related to leukostasis retinopathy are blurred vision, diplopia, restricted visual field, and the sensation of seeing floating spots (Bintoro, 2019). Clinical manifestations of leukostasis retinopathy that appear on fundoscopy due to direct neoplastic cell infiltration include Roth spots, optic nerve edema, and perivascular sheaths. Meanwhile, manifestations due to the secondary effects of hyperleukocytosis include retinal hemorrhages (dot-shaped, flame-shaped, intraretinal, subretinal, and subhyaloid), retinal vein tortuosity, retinal vein obstruction, cotton-wool spots, neovascularization and microaneurysms. peripheral, detachment of the retinal layer (serious retinal detachment) (Bintoro, 2019).

In this case, the patient came with complaints of blurred vision and diplopia. On funduscopic examination, the II nerve papillae showed blurry boundaries in all quadrants, the color of the slight was hyperemic, the peripapillary ODS was positive for bleeding, there were no ODS roth spots and exudates, ODS was bleeding with flame-shaped in 4 quadrants, vascular tortuosity was found on the ODS, and the veins were dilated. The results of this examination illustrate that the patient's leukostasis retinopathy was caused secondary to the effects of hyperleukocytosis.

Leukostasis retinopathy can occur due to hyperleukocytosis. The management principle for hyperleukocytosis with suspected leukostasis retinopathy is identifying patients at high risk by carrying out a holistic history of symptoms involving respiratory, cardiovascular, central nervous, vision and hearing, comprehensive laboratory and supporting examinations, carrying out supportive therapy and reducing the number of neoplastic cells in the circulation (Belay, Yirdaw and Enawgaw, 2017; Vicini *et al.*, 2021). Supportive therapy includes hydration, therapy to reduce concentrations of uric acid, potassium, phosphate or increase calcium. Hydration therapy is given 2-3 liters/day. Hydration aims to help reduce cell viscosity, and concentrations such as uric acid, potassium, and phosphate and improve blood flow to the kidneys and kidney filtration (Laurenti, Sica, and Pagano, 2017).

In this case, the patient was consulted by an eye colleague, and a funduscopic examination was carried out due to suspicion of leukostasis retinopathy, and laboratory examinations were carried out starting from complete blood count, electrolytes, liver function, kidney function and hemostasis function. The patient experienced hypotension, and laboratory results showed hyperuricemia, hyperkalemia, and AKI, so the patient was immediately given fluids for rehydration, Nacl 0.9% 1000 cc in 1 hour, and 1000 cc/24 hours, administration of allupurinol, correction of hyperkalemia, and transfusion was postponed until the hemodynamic condition was stable with close monitoring of vital signs and urine. In response to therapy within 24 hours, the patient's hemodynamic condition improved with blood pressure 100/68,

pulse 100x/meit regularly, and AKI improved, creatinine value became 0.7mg/dl. On day 2, potassium returned to normal to 4.7mg/dl and uric acid to 4.2mg/dl.

Apart from that, treatment of leukostasis retinopathy is by using cytoreduction agents. Cytoreduction agents include chemotherapy drugs that are recommended for every type of blood cancer. Hydroxyurea is recommended as induction chemotherapy and bridging therapy in conditions of leukostasis where the type of cancer has not been established. The recommended dose of hydroxyurea is 50-100 mg/kg (Laurenti, Sica, and Pagano, 2017; Christoph, 2015; Ranti *et al.*, 2020).

In this case, the diagnosis of CML patient with BCR ABL had been confirmed so initial treatment was given 2000 mg hydroxyurea and 1600 mg imatinib. The patient responded well to these two cytoreduction agents, within 48 hours leukocytes were reduced by 61,000 cells. On the 8th day of treatment until now the patient complained that the patient's vision had improved, the patient's visual acuity examination had improved to 6/20, the dipoplia examination was negative. However, on the 5th day of treatment, hydroxyurea was stopped because the HB fell again and thrombocytopenia occurred.

Leukapheresis is currently also a recommended cytoreduction procedure. The term leukapheresis comes from the Greek "to take away" or "to remove." Leukapheresis is based on the principle of rapid mechanical removal of excess leukocytes (Christoph, 2015). This action can reduce the number of leukocytes by 10% -70%. However, this action is still being debated. Several retrospective studies have shown that there is no difference in the benefits of performing or not performing leukapheresis. And other studies show that there is no correlation between preventing leukapheresis and the risk of early death in cases of leukostasis or tumor lysis syndrome (Choe et al., 2018; Rosales et al., 2022). The use of this procedure requires caution during the procedure regarding complications of the procedure such as paresthesia due to hypocalcemia, oxygen saturation, and the occurrence of coagulopathy. Contraindications for this procedure include cardiovascular comorbidities, kidney disorders, coagulation disorders, and unstable hemodynamic conditions (Christoph, 2015; Rosales et al., 2022).

In this case, the patient presented with hypotension, acute renal impairment, and coagulation disorders with APTT lengthening to 48.6 seconds so the cytoreduction agents used were hydroxyurea and imatinib, which has been continued to date with imatinib. A case study conducted by Gupta et al (2021) showed that leukostasis retinopathy improved with imatinib without leukapheresis. Another case study also reported that patients with intracranial bleeding due to leukostasis in CML who were contraindicated with leukapheresis had an improved response to imatinib (Wang et al., 2020).

Prognosis in CML aims to determine the effectiveness of therapy against *outcome* patients. prognosis used by *Sokal*, and *Hansford* these three criteria are classified into low risk, medium risk, and high risk. Low risk implies that the therapy used is effective and causes good clinical and laboratory outcomes and vice versa in groups with high risk (Neighbors *et al.*, 2021). The prognosis for leukostasis retinopathy is generally good with visual improvement if the underlying disease is treated adequately and early. Leukostasis retinopathy requires intervention in moderate and severe cases. The intervention was carried out with radiotherapy (Belay, Yirdaw, and Enawgaw, 2017; Vicini *et al.*, 2021).

In this patient, the first day of admission to the hospital is the value *Sokal* 3.1, *Hansford* 1989, and *eutos* 111. This value is categorized as high risk and when the patient is planned

outpatient care is the value *Sokal* 0.6, *Hansford* 490, and *Eutos* 51 are included in the low-risk group. Clinically the patient improved, he no longer had blurred or double vision.

CONCLUSION

A case has been reported of a patient who had been diagnosed with CML with a positive BCR ABL who came to the oncology clinic with suspicion of leukostasis retinopathy. Leukostasis retinopathy is characterized by complaints of sudden visual disturbances, which can cause blindness and the condition of leukostasis itself. associated with thromboembolic events, neurological complications, and respiratory complications. This condition requires comprehensive and aggressive management to reduce morbidity and mortality, namely identifying patients at high risk by carrying out a holistic anamnesis for symptoms involving respiratory, cardiovascular, central nervous, vision, and hearing, comprehensive laboratory and supporting examinations, carrying out supportive therapy and reducing the number of neoplastic cells in the circulation.

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