



Leukemic Retinopathy Mimicking Cytomegalic Virus Retinitis Ending in Total Blindness from Tumor Lysis Following Local Corticosteroid and Salvage Chemotherapy

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Abstract: Authors present a 15-year-old adolescent who recently received chemotherapy for T-cell acute lymphoblastic leukemia. The bilateral visual decrease resulted from diffuse superficial perivascular hemorrhages. The clinical impression was cytomegalovirus retinitis. The patient did not respond to antiviral therapy and polymerase chain reaction for cytomegalovirus in the blood was negative. Two weeks later, the hemorrhages have started to fade revealing diffuse perivascular creamy subretinal infiltrates by funduscopy and OCT. Following salvage chemotherapy and sub-tenon corticosteroid, subretinal infiltrates decreased markedly, the subretinal fluid in the macular region resolved and vision improved bilaterally. Optic disc swelling increased and two days after a second periocular corticosteroid, visual acuity dropped from CF near the face and 20/200 to NLP bilaterally with marked resolution of the retinal and disc tumor. The tumor regression resulted from autoinfarction with vascular compromise or treatment induced tumor lysis. two weeks later, the patient succumbed.

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1. Introduction:

T-cell acute lymphoblastic leukemia (ALL) is an uncommon aggressive hematologic malignancy with a propensity to involve extramedullary organs, particularly the mediastinum and the central nervous system (Litzow& Ferrando, 2015). Authors present the case of an adolescent who presented with diffuse retinal hemorrhages initially mistaken for cytomegalovirus (CMV) retinitis and who developed total blindness from the sequelae of leukemic infiltration to the retina and optic nerve head.

2. Case Presentation:

This 15-year-old teenage boy, previously healthy, presented with fever and chest pain and received the clinical and radiologic diagnosis of severe pneumonia. He was treated with intravenous antibiotics to no avail. Repeat chest X-ray showed pleural effusion. The pleural fluid evaluation showed suspicious cells (blast like). The diagnosis changed to lymphoma. He received chemotherapy (Hyper CVAD protocol: cyclophosphamide, vincristine, Adriamycin, and dexamethasone alternating with high-dose methotrexate and cytarabine).

The patient condition worsened with new findings of severe hepatosplenomegaly and severe leukocytosis. He underwent splenectomy. He was referred to our emergency department for further management. Upon admission, he

had very high white blood count of 500,000 cells/mm³ with 90% blasts. He was started on intravenous corticosteroids, hydration, and alkalinization along with oral allopurinol. He underwent two sessions of leukoreduction. Flow cytometry (on peripheral blood) established the diagnosis of T-cell ALL. Molecular studies were negative for the common translocations. He was started on ALL induction chemotherapy as per Total 15 protocol (St. Jude Children's Research Hospital (SJCRH) protocol).

Subsequently, he complained of blurred vision in his left eye and initial Ophthalmology consult detected bilateral scattered retinal hemorrhages attributed to severe thrombocytopenia (platelet count of 51,000 per microliter; white blood count 900/mm³, and hemoglobin 9.9g/100ml). On this protocol, the patient demonstrated significant clinical improvement and morphologic remission on bone marrow aspiration. But on induction twenty-seven days after initial chemotherapy, he developed fever and diarrhea (Rota virus infection) which resulted in a delay in chemotherapy for few days. Ten days after the last induction, he developed severe bronchitis, along with a new complaint of bilateral visual loss.

CT brain and orbits did not reveal any thickening of the optic nerves or other CNS pathology. Visual acuity was hand motion in the right eye and finger counting near face in the left eye. Diffuse superficial retinal hemorrhages



covered most of the posterior pole with mild disc elevation and serous elevation of the entire macular area. Cytomegalovirus (CMV) retinitis was suspected and he was referred to the Retina Clinic (Figure 1). Two retina specialists also favored the diagnosis of CMV retinitis over leukemic retinopathy. Intravenous ganciclovir was initiated. Blood CMV polymerase chain reaction (PCR) was negative.

After two weeks, leukemic infiltration was evident by funduscopy and optical Coherence Tomography (OCT) (Figure 2). Visual acuity had improved to finger counting near face in the right eye and finger counting at 5 m in the left eye. Retinal hemorrhages have resolved revealing diffuse subretinal infiltrates. Bone marrow aspiration showed marked reappearance of blasts. The patient was shifted to the second line of treatment (ALL R16, a novel amonafide analogue), then a third line treatment (Ida FLAG, i.e. idarubicin, fludarabine, cytarabine, Granulocyte-Colony Stimulating Factor (G-CSF)) but failed to show any response.

The retina initially showed a decrease in the subretinal infiltrates with flattening of the fovea, following both the change in the chemotherapy protocol together with the first sub-tenon injection of methylprednisone acetate (Figure 3). Visual acuity improved to finger counting 60 cm right eye and 20/200 (6/60) left eye. Of particular note was the optic nerve swelling that had increased appreciably (Figure 3). Because of good clinical response, a second sub-tenon injection was given. Two days later, the patient reported a total loss of vision to no light perception. The exam revealed nonresponsive mid-dilated pupils with a resolution of disc edema and retinal infiltrates (Figure 4). The clinical impression was therapy-related tumor lysis or auto-infarction. The patient died ten weeks after the initial retina consult.

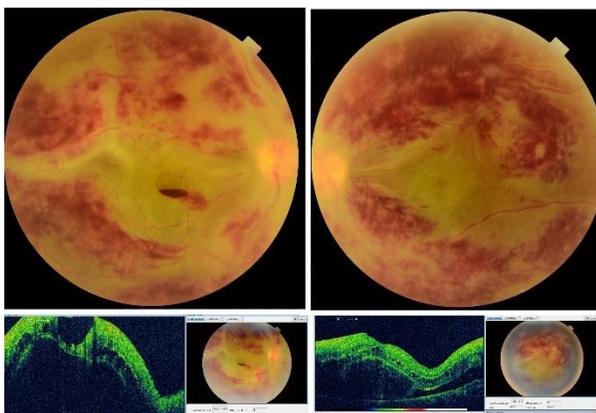


Figure 1. Initial fundus and optical Coherence Tomography OCT appearance (left photos represent the right eye; right photos represent the left eye). There are diffuse superficial perivascular retinal hemorrhages with underlying creamy looking retina suggesting CMV retinitis. Visual acuity was

hand motion in the right eye and counting finger near face in the left eye.

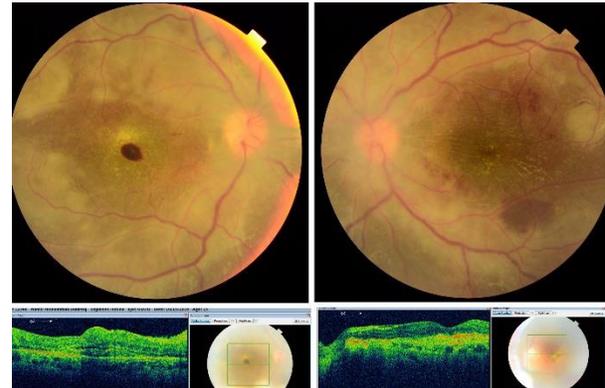


Figure 2. After two weeks of ganciclovir therapy, the retinal hemorrhages have cleared showing thickened retina by creamy infiltrates. OCT demonstrates subretinal leukemic cells.



Figure 3. The macula has flattened with residual subretinal infiltrates (following salvage chemotherapy and sub-tenon corticosteroid). Note that the optic nerve swelling has increased. Visual acuity improved to finger counting at the 60-cm right eye and 20/200 left eye.

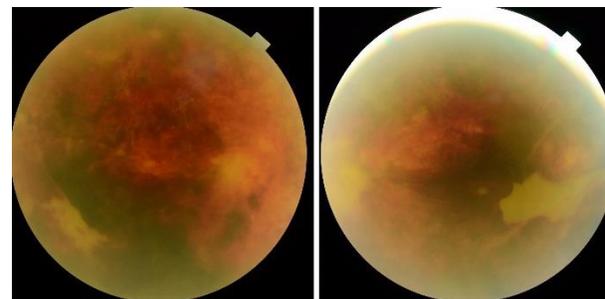


Figure 4. Regression of tumor infiltration of the disc and retina with total loss of vision in both eyes two days after the second sub-tenon corticosteroid injection. The patient died two weeks later.



3. Discussion:

The retinal findings in leukemia result from hematologic or immunosuppressive sequelae of chemotherapy (anemic retinopathy or CMV retinitis (Chawla et al., 2005; Chan et al., 2005; Amer et al., 2013; Méndez & Gil, 2014; Iwami et al., 2015) and also from leukemic infiltration (Sharma et al., 2004). Clinically it is difficult to distinguish intraocular leukemia from CMV retinitis (Levinson et al., 2008). Hence several reports performed retinal biopsy as a means of establishing the diagnosis (Gooi et al., 2008; Subramanyam et al., 2011; Johnson et al., 2015; Cerdà-Ibáñez et al., 2016) while others relied on PCR for CMV and cytology of the vitreous samples (Levinson et al., 2008; Tyagi et al., 2015).

Leukemic retinopathy manifests as infiltrative disease and/or hemorrhagic retinopathy. The infiltrates are usually perivascular, especially involving the inner retinal layers and with subretinal fluid (Sharma et al., 2004). Familiarization with these findings can enhance clinical skills in differentiation between CMV retinitis and leukemic retinopathy allowing prompt therapy with a subsequent higher chance for systemic and ocular salvage. It is noted that a negative PCR for CMV in the blood does not rule out CMV retinitis as noted by Smith et al. (1999). OCT is a new tool that can help in documenting retinal detachment and subretinal infiltrates. The features favoring leukemic retinopathy over CMV retinitis include: retinal detachment, retinal thickening, and subretinal infiltrates while CMV retinitis is characterized by a demarcation line (Wakai et al., 2013; Siedlińska et al., 2013).

The patient's visual acuity and fundus appearance improved transiently after salvage therapy and periocular corticosteroid. However, the sudden downhill course ending in total blindness can be explained by either progressive optic nerve infiltration resulting in auto-infarction or tumor lysis. Amer et al. (2013), described the case of a 25-year-old man with T-cell ALL who had a relapse. After salvage chemotherapy, the patient succumbed to tumor lysis syndrome and septicemia. Additional cases of ALL tumor lysis have been described (Benekli et al., 1996; Konuma et al., 2008; Simangan & Kline, 2015). Also, Lerza et al. (2002), described a 60-year-old woman who developed tumor lysis after systemic dexamethasone. It is possible that sub-tenon corticosteroids were involved in the lysis of tumor cells at the optic nerve head. On the other hand, several cases of central retinal artery occlusion with or without combined central retinal vein occlusion have been described when leukemic cells infiltrated the optic nerve head (Badelon et al., 1986; Chan et al., 2005; Méndez & Gil, 2014; Iwami et al., 2015; Borges et al., 2015;), favoring the theory of compressive auto-infarction at the intra-scleral optic nerve (tight compartment).

The recent use of intensive combination chemotherapy protocols in adolescents and young adults has somewhat improved the outcome of patients with T-

ALL (Litzow & Ferrando, 2015). Due to the existence of a blood-brain barrier to some chemotherapy agents, special therapy to the CNS and posterior pole of the eye is usually advocated. Hence this standard management of leukemic infiltrates of the retina and optic nerve head can include the intrathecal chemotherapy, local radiotherapy and various salvage therapies (Camera et al., 1993; Kaikov, 1996). Such therapies may lead to regression of the ocular infiltrates, but often do not improve visual acuity (Kaikov, 1996; Siedlińska et al., 2013), or the improvement in vision is transient (current case) being limited by the recurrence of the infiltrates.

4. Conclusion:

Authors emphasize the role of the ophthalmologist in the management of leukemia (Sharma et al., 2004). It is possible that early recognition of leukemic retinopathy signs by fundoscopy and OCT, followed by prompt treatment with salvage chemotherapy (and/or radiotherapy or intrathecal chemotherapy) could improve the likelihood of visual recovery and prolong survival (Kaikov, 1996). However, T cell ALL can be aggressive and unresponsive to the most current protocols, hence the search for more effective chemotherapeutic agents.

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Conflicts of Interest:

No conflicting relationship exists for any author.

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