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Recurrence of Lymphoblastic Leukemia Manifesting as Bilateral Optic Disk Neovascularization During Complete Clinical Remission--Case Report

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Abstract: *Background*: The intraocular manifestations of leukemia are diverse. The retina is the most common ophthalmic involvement site. The most common retinal manifestations of acute lymphoblastic leukemia (ALL) include dilated and tortuous vessels, serous retinal detachment (SRD), intraretinal hemorrhages as well as roth spots. Optic nerve infiltration and retinal neovascularization are unusual, especially in complete clinical remission of ALL. However, neovascularization in optic disk has not been observed in ALL during complete clinical remission. *Objective*: To report clinical characteristics of a bilateral optic disk neovascularization associated with relapse of ALL. *Method*: A 31-year-old male with ALL after having reached complete remission from chemotherapy complained about a vision loss in both eyes. First examination showed that best corrected visual acuity (BCVA) was 20/200 for his right eye and 20/160 for his left eye, respectively. Fundus examination revealed bilateral profound optic disk edema with multiple yellow-white exudates and retinal hemorrhages. Optical coherence tomography (OCT) showed bilateral optic disk edema and SRD in both maculas. Fundus fluorescein angiography (FFA) showed bilateral optic disk neovascularization. All these changes were present in remission. The patient received intravitreal Conbercept injection 0.5 mg (10 mg/ml) in both eyes for once on June 29, 2019. Optic disk neovascularization resolved three weeks after treatment. BCVA improved to 20/200 in his right eye, but still light perception in his right eye. No optic disk neovascularization recurrence was observed in 3-month follow-up. BCVA of the right eye maintained 20/200 at the latest follow-up. After intravitreal injection for 4 months the patient suffered from cerebral hemorrhage. He received bone marrow biopsy and cerebrospinal fluid sampling. The results showed relapse in hemogram and lymphocytes in central nervous system (CNS). Therefore, the chemotherapy treatment did not cause a new remission of the disease and the patient failed to recover. *Conclusion*: Optic disk neovascularization may appear as a sign of extramedullary relapse of ALL months in advance of the hematologic relapse. Intravitreal injection of conbercept could be beneficial and safe in treating this neovascularization.

Keywords: Acute Lymphoblastic Leukemia, Optic Disk Neovascularization, Anti-vascular Endothelial Growth Factor, Recurrence

1. Introduction

Ocular manifestations of leukemia have been reported to occur in up to 90% of leukemic patients and are one of the significant causes of visual disturbance. The retina is the most commonly site of involvement. Leukemic retinopathy includes dilated and tortuous vessels, intraretinal hemorrhage, white-centred hemorrhage (roth spots) and serous retinal detachment (SRD). These complications usually occur when patients present with clinical and hematological symptoms, and are less common during complete remission [1, 2]. The swollen disk due to infiltrative optic neuropathy has been reported in literature [3-5]. However, optic nerve infiltration combined with optic disk neovascularization is rare, it has not been reported until now. We report a case of recurrent ALL, presenting as bilateral optic nerve infiltration and optic disk

neovascularization in complete clinical remission.

2. Case Presentation

A 31-year-old man was referred to the ophthalmology clinic of Nanning Aier Eye Hospital on April 23, 2019, complaining of bilateral acute visual loss coursing for three months, without ophthalmodynia and headaches. He denied diabetic mellitus or any other systemic symptoms, and repeating blood pressure was normal. Ophthalmological examination BCVA was 20/200 for his right eye and 20/160 for his left eye. Intraocular pressure in bilateral was normal. Slit-lamp examination of the anterior segment and vitreous were unremarkable. Up to 200 degrees of the retina were captured in one Optomap® ultrawide field scanning laser ophthalmoscope (UWF SLO) image revealed bilateral profound optic disk edema with multiple yellow-white exudates, tortuous vessels, peripapillary flame-shaped hemorrhages (Figure 1). Additionally, Optical coherence tomography (OCT) demonstrated bilateral optic disk edema and SRD which did involve both the maculas (Figure 2). We suggested the patient receive cranial and orbital magnetic resonance imaging (MRI) to eliminate intracranial space-occupying lesions, and magnetic resonance venography (MRV) to eliminate cerebral venous sinus thrombosis (CVST). MRI did not show any sign of cranial mass and MRV was also normal.

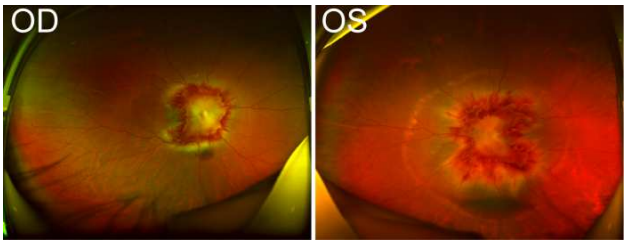

Figure 1. *Ultrawide field scanning laser ophthalmoscope image (first visit) demonstrating bilateral massive optic disk edema, multiple yellow-white exudate, tortuous vessels, peripapillary flame-shaped hemorrhages and serous retinal detachment.*

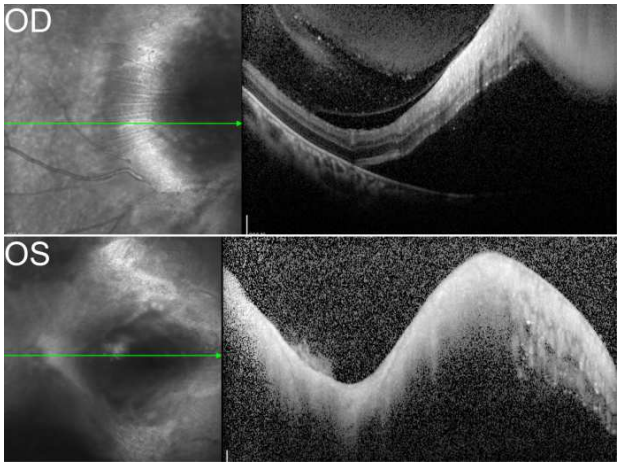

Figure 2. *Optical coherence tomography images demonstrating optic disk edema and large amount of submacular fluid in both eyes.*

In the meantime, the patient presented with further deterioration of vision. BCVA was 20/400 in his right eye and count fingers in his left eye, respectively. Fundus fluorescein angiography (FFA) showed neovascularization of papillary hyperfluorescence in both eyes during all the phases of the examination (Figure 3). Serology for opportunistic infections was negative. On complete blood count, his eosinophil count increased abnormally up to 3.7×10^9/L (normal $0.02\text{-}0.5\times10^9$/L), and the percentage of eosinophil was 40.5% (normal 0.5-5.0%). At the time of presentation, he admitted that he had been diagnosed with ALL two years ago and received chemotherapy and central nervous system (CNS) prophylaxis with intrathecal chemotherapy. After ALL in remission for five months, he complained of impaired vision in both eyes, then visited the hematology department of local hospital. He received bone marrow biopsy and lumbar puncture respectively, the results showed absence of relapse in hemogram and the normal opening pressure. Cerebrospinal fluid sampling was performed, and no leukemic infiltration was observed. In view of patient's age and personal pathological history, the first suspicion was from the beginning infiltration due to ALL-T.

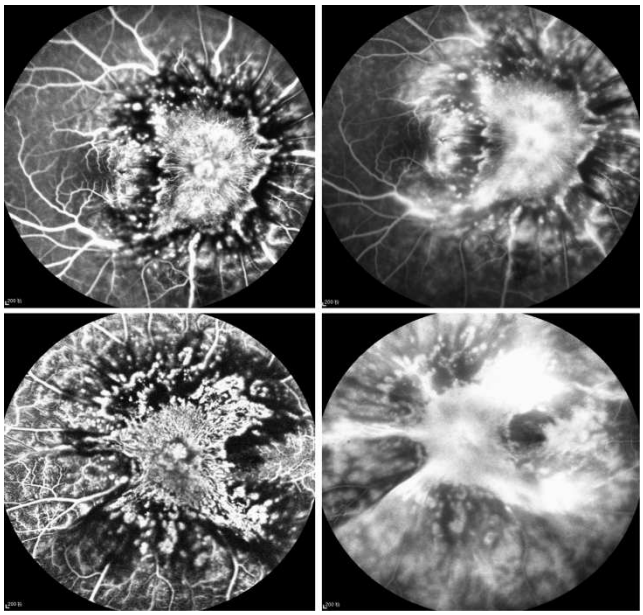

Figure 3. *Fluorescein angiogram demonstrating bilateral peripapillary petal-shaped hyperfluorescence of neovascularization at early stage and neovascularization leakage at late stage.*

3. Outcomes

Five months after initial presentation, the patient's BCVA was decreased to count fingers in his right eye and light perception in the left eye. Fundus examination revealed optic disk exudation and retinal hemorrhages were enlarged in both eyes, especially in his left eye (Figure 4). He received intravitreal injection of conbercept (Konghong Biotech) 0.5mg (10mg/mL) in both eyes for once on June 29, 2019. Three weeks following ophthalmological treatment, BCVA improved to 20/200 in his right eye, but

still light perception in his left eye. Fundus examination exhibited the optic disk edema and neovascularization have lessened in both eyes, while exudative retinal detachment with no reattachment (Figure 5). After 3-month follow-up, BCVA was maintained 20/200 in his right eye and light perception in his left eye. No optic disk neovascularization recurrence was observed. Because of the strong side effects on fluorescein sodium, FFA was not performed. Lately, through telephone follow-up we were informed that the patient had suffered from cerebral hemorrhage and had to be admitted to the intensive care unit. He received bone marrow biopsy with relapse in hemogram lymphocytes in CNS involvement. The chemotherapy treatment did not achieve a new remission of the disease and he died 18 months after recurrence.

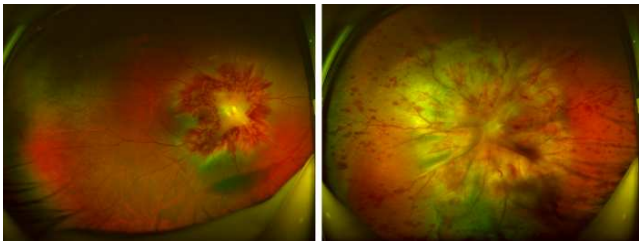

Figure 4. *Ultrawide field scanning laser ophthalmoscope image (before treatment) demonstrating bilateral retinal flame-shaped hemorrhages enlarged, serous retinal detachment involved the entire retina of the left eye.*

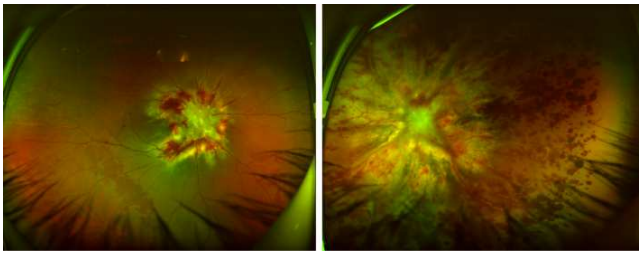

Figure 5. *Ultrawide field scanning laser ophthalmoscope image (3 weeks after intravitreal injection) demonstrating optic disk edema was lightened and neovascularization disappeared in both eyes, serous retinal detachment was still exist in the left eye.*

4. Discussion

Isolated ocular involvement as the first sign of relapse is extremely rare, occurring in less than 2.2% of cases [6]. Optic disk neovascularization is rarely found associated with ALL. To our knowledge, it is the first report demonstrating that bilateral optic nerve infiltration and optic disk neovascularization can be a manifestation of ALL recurrence. Optic nerve infiltration and optic disk neovascularization can appear as an isolated sign of ALL-T extra-medullar relapse, preceding in even several months the hematological relapse.

Optic nerve infiltration may be induced by leukemic cells to play a causative role in visual decline. The optic nerve can reveal malignant cell invasion of the CNS, which occurs more frequently in acute than chronic leukemia [1, 5]. Optic nerve infiltration can occur with lymphocytic or myelogenous leukemia as an early or late sequel [4, 7]. The pathogenesis of optic nerve edema is not fully understood, but this study maybe serve as obstruction of venous outflow by perivascular leukemic cells [8]. Retrolaminar leukemic invasion or by direct optic infiltration of the optic nerve head leading to increase in vascular permeability may also contribute to optic disk edema [1, 9]. It has been suggested that leukemic retinopathy may indicate aggressive disease and poor prognosis [1].

The pathological mechanism of leukemia cells infiltration leading to optic disk neovascularization is unclear. Leukemia cells in chronic ALL secreted excessive vascular endothelial growth factor (VEGF), and VEGF receptor 1 and/or VEGF receptor 2 receptors were overexpression, which may be vital for the occurrence and development of neovascularization [10, 11]. The patient's visual symptoms occurred in complete clinical remission, but had developed severe myelosuppression which aggravated the hypoxia-ischemia in fundus that may be related to more VEGF production and neovascularization [12]. VEGF/VEGF-receptor interaction was involved in proliferation and migration, which might be critical for hematological relapse [13].

Studies about the beneficial and safe of intravitreal injection are scarce. Pour et al [14] reported a 45 year old man with leukemia who developed choroidal neovascularization (CNV) in macular, the CNV rapidly resolved after intravitreal injection of bevacizumab, vision recovered and no recurrence or complications were observed. Our case also demonstrated that anti-VEGF agents regressed optic disk neovascularization in patients with leukemia, and visual acuity improved after intravitreal injection of conbercept.

Following a period of 3-month dynamic observation after intravitreal injection. BCVA was maintained 20/200 in his right eye and light perception in his left eye. Eight months after initial presentation, through telephone follow-up we were informed that the patient had suffered from cerebral hemorrhage and had to be admitted to the intensive care unit. The patient was confirmed hematological relapse and revealed lymphocytes in CNS involvement. The chemotherapy treatment did not achieve a new remission of the disease and he did not recover.

5. Conclusion

For ophthalmologists, optic disk neovascularization must be kept in mind as a rare ophthalmic manifestation of patients with ALL even in the remission phase. The presence of neovascularization correlated with poorer survival for patients with ALL. Meanwhile, the treatment of intravitreal injection of Conbercept in optic disk neovascularization was also beneficial and safe in patient with ALL.

Patient Consent

Written informed consent was obtained from the patient's wife for publication this report.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Aier Eye Hospital Group and complied with the Helsinki Declaration. The patient and his wife signed the written informed consent.

Competing Interests

The authors declare that they have no competing interests.

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