A Significant Finding in Acute Lymphoblastic Leukemia: Bilateral Serous Retinal Detachment

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a rare hematopoietic neoplasia in adults. Although fundus changes are common in the course of the disease, serous retinal detachment may occur without retinopathy.

The patient, who was being followed-up with the diagnosis of Pre-B ALL, had two allogeneic bone marrow transplants, developed Graft-Versus-Host disease after peripheral blood stem cell transplantation, and had a history of ruxolitinib and high-dose dexamethasone usage, was consulted with decreased visual acuity while hospitalized in hematology clinic due to necrotizing fasciitis on his foot. Intrathecal chemotherapy and dexamethasone treatment were recommended to the patient who had a bilateral serous macular detachment in ophthalmologic examination and leukemic infiltration of the choroid that was suspected in his ocular imaging. It was observed that the patient's vision improved, and the serous detachment regressed after the addition of dexamethasone to ongoing ruxolitinib treatment. Serous retinal detachment is a rare finding in ALL. This finding may indicate choroidal infiltration and poor prognosis. Therefore, early diagnosis and treatment are very important to improve the prognosis.

Keywords: Acute lymphoblastic leukemia, serous macular detachment, leukemic infiltration, Graft-versus Host, peripheral blood stem cell transplantation.

INTRODUCTION

Acute lymphoblastic leukemia (AKK) is a malignant neoplasm characterized by monoclonal proliferation bone marrow hematopoietic stem cells. It is rarely seen adults and has poorer prognosis compared to pediatric patients[1].

Ocular involvement has been reported in ALL patients up to 90% of cases[2]. The involvement can be direct leukemic infiltration or secondary hematological abnormality, hyperviscosity, chemotherapy and opportunistic infections[2]. In these patients, retina is the most commonly involved ocular structure and hemorrhage is the most commonly detected retinal finding which is generally related to anemia and thrombocytopenia[2, 3]. Micro-aneurysm, cotton wool appearance, venous dilatation and increased tortuosity, vascular sheath and leukemic infiltrates can be seen in addition to hemorrhage in the fundus examination[2]. Serous retinal detachment and optic disc edema are rare findings[3].

Here, we aimed to outcomes of follow-up and treatment in the patient with preB-ALL who developed acute loss of vision and bilateral serous macular detachment but not clinical vascular findings.

Case Report

A 56-years old man was referred to us by hematology department for impaired vision in both eyes over 4 days. In the history, it was found out that the patient was diagnosed as high-risk pre-B ALL 11 months ago and that he received HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy regimen; followed by allogeneic bone marrow transplantation, and achieved complete remission with minimal residual disease. It was also found out that the patient had recurrent disease during follow-up after first transplantation and allogeneic stem cell transplantation was repeated 3 months ago; thereafter, he also received peripheral hematopoietic stem cell transplantation since recurrence was detected on month 2 after second transplantation. As the patient experienced fever and erythematous skin lesion in both feet during follow-up after peripheral hematopoietic

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stem cell transplantation, he underwent skin biopsy with initial diagnosis of Graft-versus-Host disease (GVHD), confirming the diagnosis of GVHD. Thus, dexamethasone (96 mg) and ruxolitinib were given. One month after onset of GVHD, necrotizing fasciitis was developed at his foot and he was admitted to hematology department and dexamethasone therapy was halted.

In ophthalmologic examination, best-corrected visual acuity was found as finger counting at 2 meters in both eyes. The intraocular pressure was measured as 15 mmHg in the right eye and 17 mmHg in the left eye. No cell was detected in anterior chamber and vitreous on biomicroscopic examination. In fundus examination, serous macular detachment involving arcuate was observed in both eye (Figure 1A, B). On EDI-OCT, serous macular detachment with increased choroidal thickness (715 µm) was detected (Figure 1C, 1D). On fluorescein angiography, it was observed that area of serous detachment was hypo-fluorescent with hyper-fluorescent areas at margins of serous detachment an that there was multiple, punctate increase in staining with hyper-fluorescent area and optic disc staining

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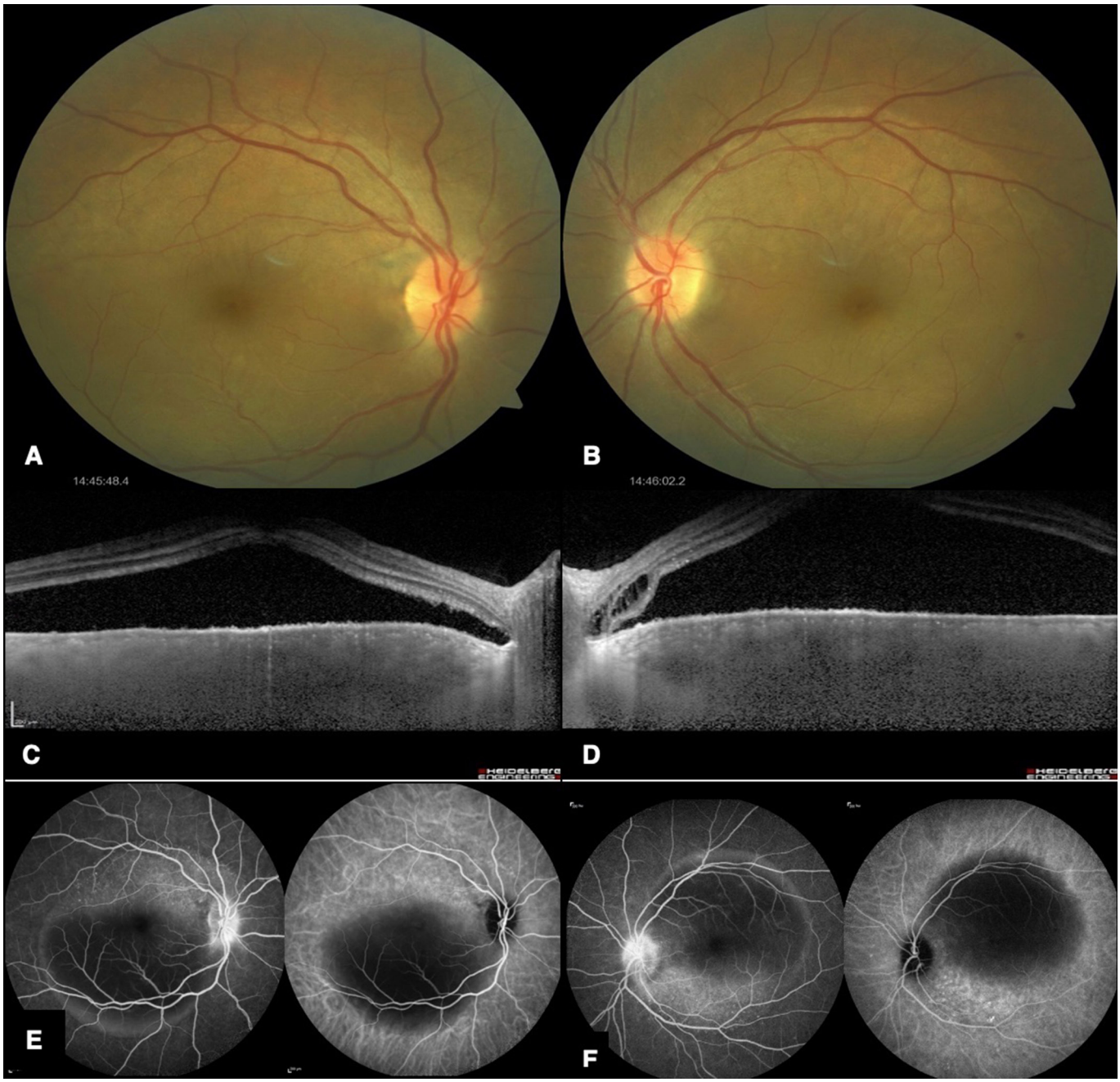

Figure 1: *Bilateral serous retinal detachment in the right (A) and left eye (B) at initial examination; choroidal thickening and macular detachment on EDI-OCT imaging (C, D) and hypo-fluorescence at areas corresponding serous detachment and surrounding punctate hyper-fluorescence on FFA and ICGA (E, F).*

in both eyes. In indocyanine green angiography (IGA), hypo-cyanine with surrounding hyper-cyanine points was observed at the area compatible to serous detachment in both early and late phase in both eyes (Figure 1, 1F). On B-mode sonography, it was seen that the choroid was thick but there was no involvement in optic nerve. Again, there was no finding of mass lesion or optic nerve infiltration on cranial and orbital magnetic resonance imaging. Given the presence of pre-B ALL I in the patient, it was suggested ophthalmologic findings were due to leukemic choroidal infiltration; however, it might be associated with rejection in the presence of history of GVHD. The initial diagnoses was reported to hematology department and intrathecal chemotherapy for leukemic choroidal infiltration and oral steroid therapy for GVHD were planned. However, dexamethasone 80 mg/day was initiated but intrathecal chemotherapy could not be initiated due to poor general status. On day 7 of treatment, BCVA was 0.4 in both eyes. In fundus examination (Figure 2A, 2B) and EDI-OCT (Figure 2C, 2D), there was marked regression in serous macular detachment and decreased choroidal thickness. During follow-up, it was observed visual acuity was improved to 0.5; however, it was found out that the patient died due to massive pulmonary hemorrhage resulting from thrombocytopenia in the next follow-up visit.

The patient gave written informed consent for medical records for academic purposes.

DISCUSSION

Retina is the most common region for involvement in ALL patients and retinal hemorrhage is the most frequent ocular finding[4]. Although retina infiltrations can be readily diagnoses, choroidal infiltration is rarely recognized in clinical practice. However, in postmortem histopathological studies, it was observed that choroid is involved in 85% of cases[5]. Choroid can lead bilateral, shallow serous retinal detachment at posterior pole when it is severe[6]; however, it was rarely reported as initial finding of leukemia.[7] In most cases, it was seen that systemic disease was detected before onset of ocular symptoms.[6] Serous retinal detachment can also appear as a finding of disease recurrence retina[8].

It is thought that serous retinal detachment develops by decreased choriocapillaris blood flow, ischemia in retinal

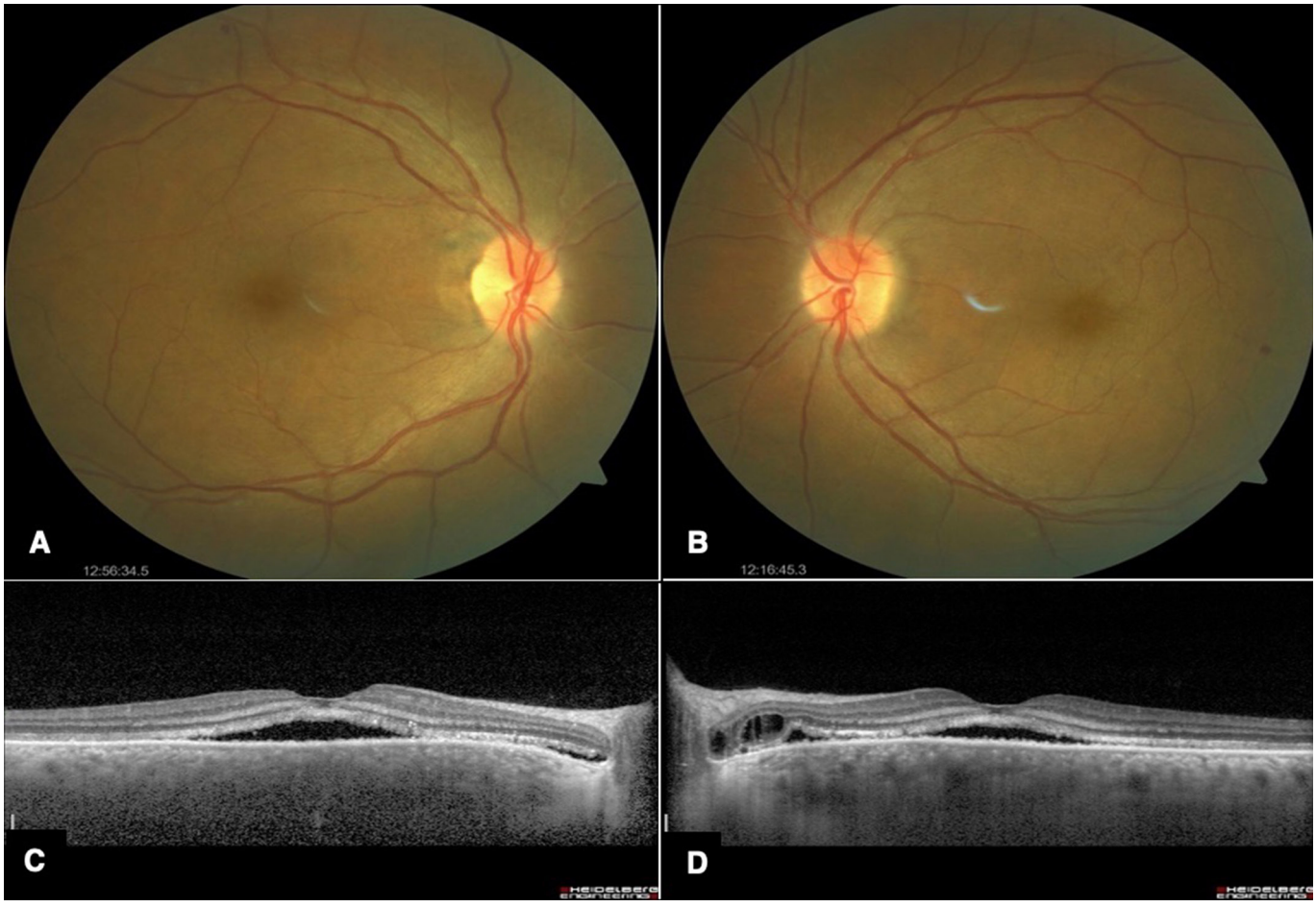

Figure 2: *Regression of serous macular detachment in both eyes in ophthalmologic examination on day 7*(A, B) *and decreased serous macular detachment and decreased choroidal thickness on EDI-OCT'de* (C, D).

pigment epithelium and outer blood-retina barrier resulting from leukemic infiltration of choroid[7, 9]. In previous studies, multifocal hyper-fluorescence at early phase and subretinal pooling at late phase were demonstrated on fluorescein angiography[10]. It is thought that this finding occurs RPE ischemia secondary to impaired circulation in choriocapillaris. Choroidal leukemic infiltration tends to be perivascular in general[11] and it was shown that choroid thickness was markedly increased in previous studies. Choroidal thickening can be demonstrated with EDI-OCT and the thickening can be a marker of leukemic choroidopathy.[12] In our case, choroid was markedly thickened on EDI-OCT and similar fluorescein angiography findings were present. In addition, optic disc leakage was observed, suggesting optic nerve infiltration. In adult patients, leukemic infiltration has been rarely reported in adult patients and it was proposed that optic nerve infiltration can be a poor prognostic marker. In the patients, optic disc edema can develop due to compression in nerve fibers due to leukemic infiltration of optic nerve, disrupted axoplasmic flow and venous outlet obstruction of perivascular leukemic cells[13, 14, 15].

The ocular findings of leukemic infiltration cannot be treated directly. Preferentially, systemic chemotherapy is recommended for underlying leukemia. Ocular radiation can be employed when leukemic infiltrates failed to respond chemotherapy[16]. Intrathecal chemotherapy is required for leukemic infiltration of optic nerve[13].

Hematopoietic stem cell transplantation including peripheral blood stem cell transplantation and bone marrow transplantation are considered as curative therapy for hematological malignancy today[17]. In the literature, two serous retinal detachment cases accompanied by optic disc edema and optic disc leakage were reported following peripheral blood stem cell transplantation and it is suggested that this finding is poor prognostic for survival[17]. In these patients, punctate hyper-fluorescent areas, hypo-fluorescent staining at the area of serous detachment on FA and choroidal thickening on sonography were observed. In our case, serous retinal detachment was considered in differential diagnosis given that there was history of peripheral blood stem cell transplantation, serous retinal detachment developed following peripheral blood stem cell transplantation and similar cases reported in the literature. In addition, regression in macular detachment suggested the diagnosis of leukemic choroidal infiltration in our patient.

GVHD is a different autoimmune condition which appears as similar to multi-focal CSCR but has pathophysiological mechanism resembling cell-mediated immune response seen in VKD[18]. In the literature, bilateral panuveitis and serous RD cases due to chronic GVHD following allogeneic bone marrow transplantation have been reported. In these cases, staining in optic disc and vascularity, multiple hyper-reflective areas were observed in fluorescein angiography while undulated, thickened RPE similar to OCT findings seen in VKD were seen on OCT. As similar to VKD, GVHD also responds systemic immune suppression by corticosteroids[19]. In our case, biopsy was performed with initial diagnosis of GVHD following onset of erythematous lesion on his foot and high-dose steroid plus roxulitinib therapy was initiated after confirmation of GVHD. However, GVHD was excluded due to lack of panuveitis which is typical for GVHD.

Our case emphasizes importance of ophthalmologic examination in leukemia patients. Recent studies suggest that patients with leukemic retinopathy have more aggressive disease and worse results. Although prognosis is poor in leukemia patients with ocular findings, early diagnosis and timely management spare vision while healing recurrent disease and leading long-term remission.

In conclusion, onset of serous retinal detachment in a ALL patient should alarm ophthalmologist about recurrence. It should be kept in mind that serous retinal detachment can be first finding of ALL. Thus, the cases with acute onset of serous retinal detachment should be comprehensively assessed for leukemia in a systemic manner.

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