OPEN ACCESS

ISSN: 2837-3642

Louise P, et al. (2025): 291
Anna Clin Rev Cas Rep, 2025; 3(4): 100148
Doi: 10.71010/ACRCR.2025-e148

Case Report

Annals of Clinical Reviews & Case Reports

Serous Retinal Detachment Secondary to Choroidal Infiltration in Acute Lymphoblastic Leukemia: A Case Report with Review of Literature

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Citation: Louise P, Ingele C, Heidi S, Julie J, Sandra J (2025) Serous Retinal Detachment Secondary to Choroidal Infiltration in Acute Lymphoblastic Leukemia: A Case Report with Review of Literature. Anna Clin Rev Cas Rep: ACRCR-148.

Received Date: 24 March, 2025; **Accepted Date:** 31 March, 2025; **Published Date:** 04 April, 2025

Abstract

We describe a case of acute lymphoblastic leukemia (ALL) presenting with unilateral serous retinal detachment (SRD), at the time of diagnosis. We aim to give an overview of the clinical characteristics of leukemic choroidopathy pre- and post-treatment and discuss its treatment implications, both lacking in current literature. In our case, shortly after initiation of therapy, the SRD completely resolved.

Keywords:
Acute lymphoblastic leukemia, serous retinal detachment, enhanced-depth imaging spectral-domain optical coherence tomography, leukemic choroidopathy

Abbreviations:
ALL, acute lymphoblastic leukemia
SRD, serous retinal detachment
CNS, central nervous system
CSF, cerebrospinal fluid
MRI, magnetic resonance imaging
ITC, intrathecal chemotherapy
EDI-OCT, enhanced-depth imaging spectral-domain optical coherence tomography
BCP-ALL, precursor B-cell ALL
BCVA, best-corrected visual acuity
RPE, retinal pigment epithelium
CSC, Central serous chorioretinopathy
VKH, Vogt-Koyanagi-Harada
VEGF, vascular endothelial growth factor

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of malignancy in children, representing approximately 25% of all childhood malignancies. Treatment of ALL consists of intensive multi-agent chemotherapy for about 2 years. Improved supportive care and optimization of therapy based on more precise risk stratification have increased long-term survival rate to 90%.

Serous retinal detachment (SRD) is a rare manifestation of leukemia. The mechanism underlying the occurrence of SRD in acute leukemia remains uncertain; however different theories have been hypothesized [1]. We are convinced that accurate diagnostic documentation of this rare condition, can bring more insight into its pathophysiology.

Involvement of the central nervous system (CNS) at presentation occurs in about 10% of adult patients with ALL, although in children this is less frequent [2]. Central nervous system involvement is evaluated by cerebrospinal fluid (CSF) assessment and imaging [3]. Ophthalmic evaluation is not always included in the initial screening, although retinal leukemic infiltration is also considered as CNS involvement, even with negative Magnetic Resonance Imaging (MRI) and lumbar puncture [4].

Retinal involvement necessitates additional intrathecal therapy because CNS involvement is associated with a higher risk of relapse. Intrathecal chemotherapy (ITC) is an important component of the prophylaxis and treatment of hematologic manifestations in the CNS. Different regimens of intrathecal chemotherapy have been formulated. The three most common IT drugs are methotrexate, cytosine arabinoside and corticosteroids. The optimal combination of these modalities has not yet been established by control trials and vary depending on whether they are used as prophylaxis or treatment [2]. In addition, several studies show higher mortality rates in children with ocular involvement compared to normal eye findings [5,6].

A prospective study of the ocular manifestations in childhood leukemia by Reddy et al. in 82 children showed that only 3 (3.6%) presented with eye symptoms, ocular changes (of any type) however were found in 14 children (17%). This number is most likely an underestimation because there was no enhanced-depth imaging spectral-domain optical coherence tomography (EDI-OCT) available during that time, complicating the diagnosis of choroidal infiltration [5].

In current literature, detailed reporting of the clinical characteristics of leukemic choroidopathy findings pre- and post-treatment is lacking. However, the above considerations endorse the need to understand and describe this rare manifestation. We also aim to give more insight in the implications of the diagnosis of leukemic chorioretinopathy on systemic treatment, based on a multidisciplinary approach between the treating pediatric oncologist and ophthalmologist.

2. Case report

We report a 15-year-old female patient with sudden metamorphopsia on the right eye, one day after hospitalization for a new diagnosis of precursor B-cell ALL (BCP-ALL) but before start of treatment. Blood count at diagnosis showed anemia, thrombopenia, neutropenia as well as blastosis. On presentation best-corrected visual acuity (BCVA) was 20/50 in the right eye and 20/25 in the left eye. Dilated fundus examination showed a small shallow abnormality serous retinal detachment in the right eye, without other retinal abnormalities (Figure 1).

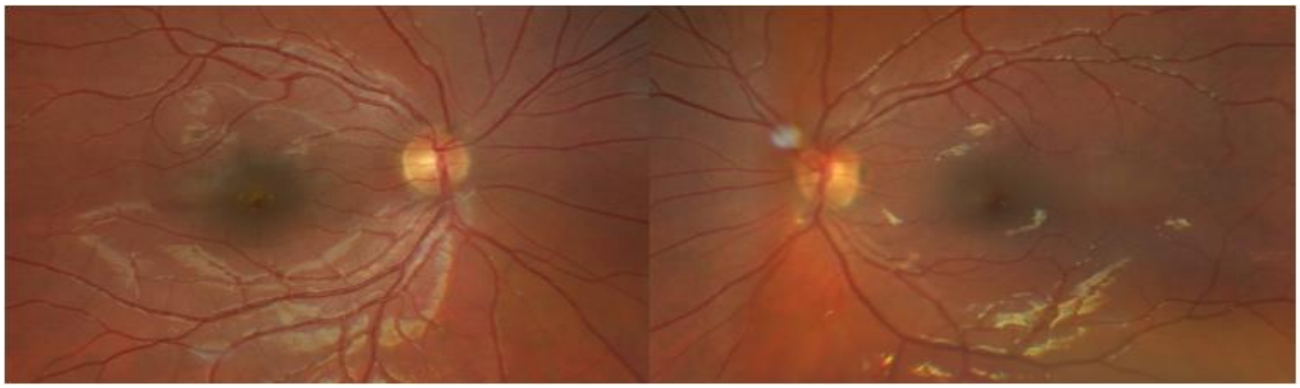

Figure 1: Fundoscopic examination at presentation, showing a small shallow serous retinal detachment in the right eye and the absence of significant abnormalities in the left eye.

Further investigations with EDI-OCT showed a unilateral SRD in the right eye with a significant increase in choroidal thickness, 689 µm and 687 µm in the right and left eye, respectively (measured subfoveally) (Figure 2a).

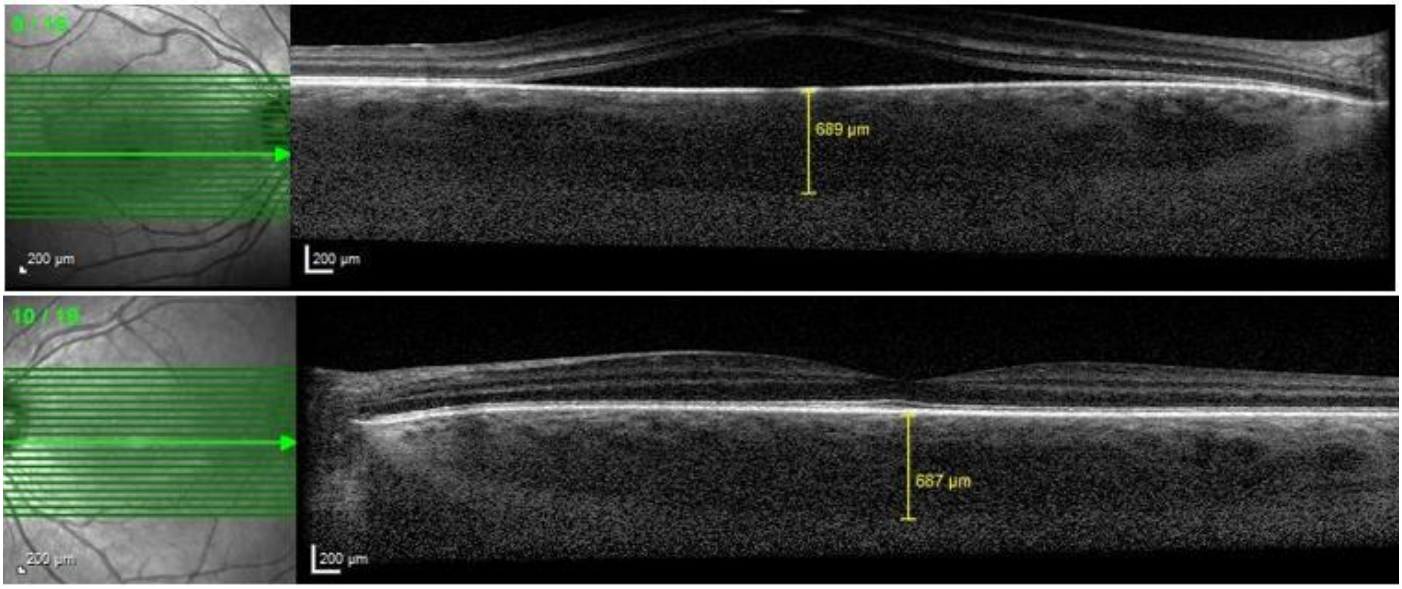

Figure 2a: EDI-OCT at presentation before start of treatment. SRD on the right eye with significant increase in central choroidal thickness (689 µm and 687 µm in the right and left eye respectively). On the right eye we can also note a discrete disruption of the retinal pigment epithelium.

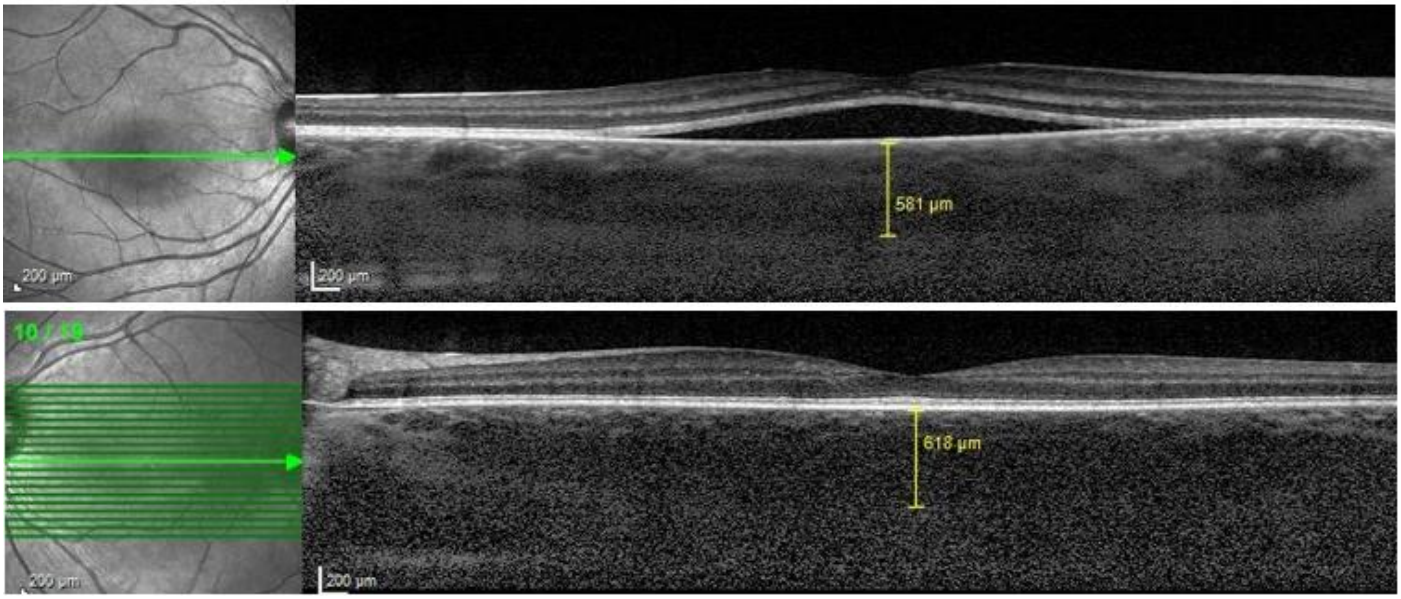

Figure 2b: EDI-OCT two days after initiation of triple intrathecal chemotherapy. Substantial reduction in central choroidal thickness of both eyes was seen (decrease of 108 µm (15,7%) and 69 µm (10,0%) in the right and left eye respectively) concurrent with the regression of the serous retinal detachment.

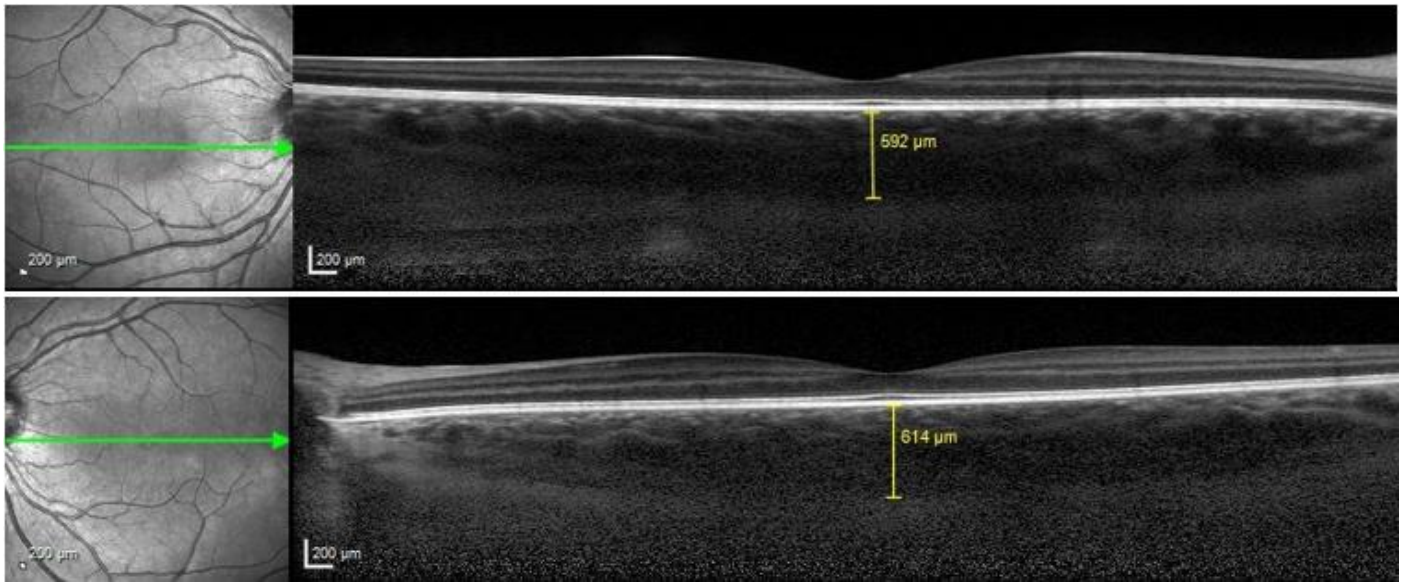

Figure 2c: EDI-OCT 124 days after first presentation, in consolidation phase of chemotherapy. A small increase in choroidal thickness was seen on the right eye (from 581 µm to 592 µm (1,9%)). On the left eye choroidal thickness remained relatively stable (from 618 µm to 614 µm (0,7%)).

Autofluorescence imaging of the right eye revealed a hyperautofluorescent region, corresponding to the zone of the SRD (Figure 3). Because of these findings we had a high suspicion of leukemic choroidal infiltration with secondary SRD formation.

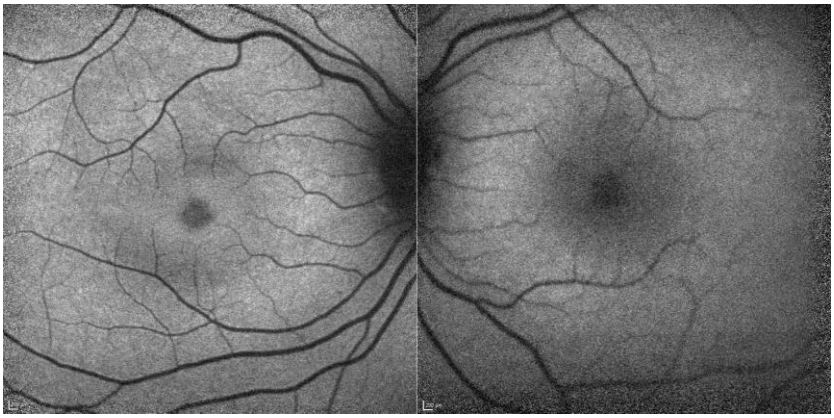

Figure 3: Autofluorescence imaging of the right eye at presentation revealed a hyperautofluorescent region, corresponding to the zone of the SRD.

Previous lumbar puncture and MRI of the brain showed no evidence of leukemic CNS involvement. However, retinal involvement indicated CNS involvement, even with a negative lumbar punction and MRI scan. CNS involvement stratified our patient to a higher risk group with intensified therapy, more specifically triple intrathecal therapy (including methotrexate, hydrocortisone, and cytarabine). Two days after initiation of treatment, significant improvement was noted, including an improvement in visual acuity and complete resolution of metamorphopsia complaints. On fundoscopic examination we saw normalization of the macular region. However, a peripheral retinal hemorrhage, also a sign of leukemic retinopathy, was observed in the right eye. EDI-OCT showed substantial reduction in central choroidal thickness (decrease of 108 µm (15,7%) and 69 µm (10,0%) in the right and left eye respectively), concurrent with the regression of the serous retinal detachment (Figure 2b). After an additional two weeks, complete resolution of the serous retinal detachment was evident. For further diagnostic confirmation and to provide a comprehensive assessment of leukemic chorioretinopathy, we also performed B-scan ultrasonography and fluorescein angiography. B-scan ultrasonography revealed an evident increase in the thickness of the sclero-choroidal complex at the posterior pole on the right eye (2.08mm-2.13mm) and (1.94_mm-2.06_mm) on the left eye (Figure 4).

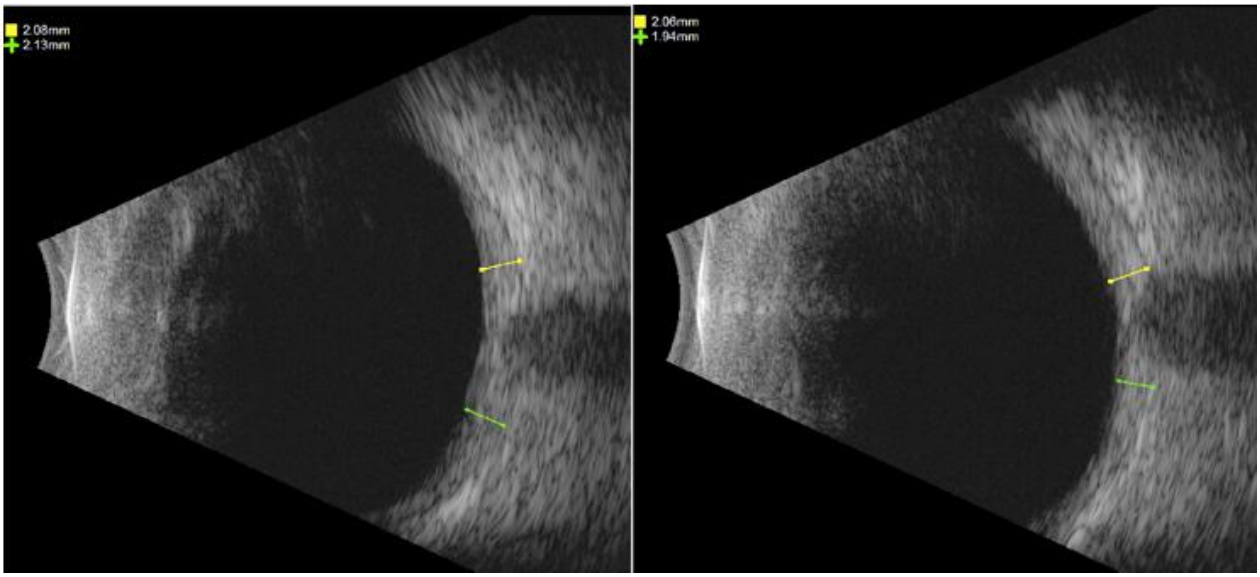

Figure 4: B-scan ultrasonography revealed an evident increase in the thickness of the sclero- choroidal complex at the posterior pole. In the right eye, the measurements ranged from 2.08 to 2.13 mm, while in the left eye, they ranged from 1.94 to 2.06 mm.

Fluorescein angiography revealed normal retinal vasculature without any signs of leakage in both eyes. In the left eye, a window defect was observed, which is probably due to retinal pigment epithelium (RPE) alterations. Indocyanine green angiography could not be performed because of iodine contrast allergy.

To compare choroidal thickness after a longer period of treatment initiation, an additional EDI- OCT was performed 124 days after first presentation. At this point, the patient was in complete remission and received consolidation chemotherapy. EDI-OCT showed no further reduction of choroidal thickness, moreover a small increase was seen on the right eye (from 581 µm to 592 µm (1,9%)). On the left eye choroidal thickness remained relatively stable (from 618 µm to 614 µm (0,6%)) (Figure 2c). Figure 5 presents a summary of these findings pre- and post-treatment.

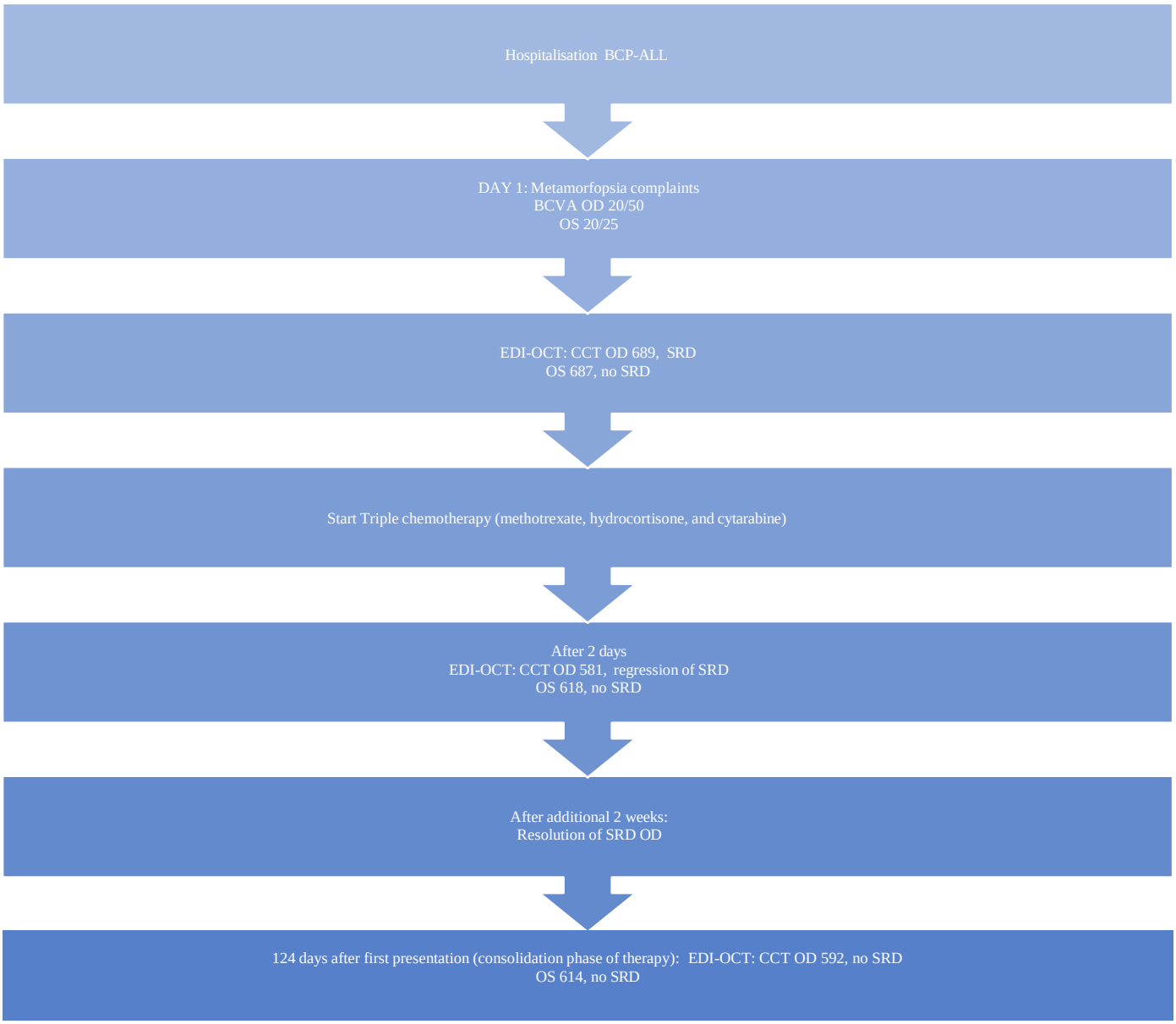

Figure 5: Summary of findings. Abbreviations: BCP-ALL, B-cell precursor acute lymphoblastic leukemia; BCVA, best corrected visual acuity; EDI-OCT, enhanced-depth imaging spectral- domain optical coherence tomography; CCT, central choroidal thickness; OD, Oculus Dexter; OS, Oculus Sinister; SRD, serous retinal detachment

3. Discussion

The choroid is interpreted as an ideal sanctuary for leukemic cells, allowing blasts survival due to the high blood flow rate and oxygen availability.[1,4] Direct invasion of the choroidal vasculature by leukemic cells results in decreased blood flow and subsequent ischemia, causing interruption of the retinal pigment epithelium tight intercellular junctions and decreased pumping ability [1,7,8,9]. In the case of severe choroidal infiltration, retinal detachment can occur [7]. This has been hypothesized as the mechanism underlying the occurrence of serous retinal detachment in acute leukemia.

There is no pathognomonic pattern of chorioretinal involvement in leukemia. Therefore, other causes of serous retinal detachment must be considered, the most important being: posterior scleritis, central serous chorioretinopathy (CSC), Vogt-Koyanagi-Harada Disease (VKH) and lupus choroidopathy, as these also significantly increase choroidal thickness [1]. Posterior scleritis was unlikely because of the absence of ocular pain. VKH could be ruled out because of normal fluorescein angiographic findings. Our patient had not been treated with corticosteroids at time of presentation, making the diagnosis of serosa centralis less likely. Moreover, in our case, resolution of the retinal detachment with chemotherapy supported our theory that the SRD was due to choroidal infiltration.

EDI-OCT is considered an indispensable tool, objectively documenting choroidal thickening, enabling repeated measurements and accurate follow-up [1]. Choroidal thickness was defined as the distance from the high reflection line of the Bruch membrane to the line of the inner surface of the sclera, measured subfoveally. In our case choroidal thickening was diffuse and extended beyond the areas of subretinal fluid. There seemed to be no correlation between choroidal thickness and the presence/extent of the SRD. We suggest that determining baseline choroidal thickness to detect early changes during follow-up could serve as a guide to predict relapse.

Previous cases described in literature typically exhibited a multifocal leakage pattern on fluoresceine angiography within the macular region as the most common angiographic finding [1]. However, this was not seen in this case. Unfortunately, ultrasonography and fluorescein angiography were only conducted after treatment was already started, because at first presentation the general condition of the patient was too bad. Thus, it could be possible that we didn't see the leakage because treatment was already initiated at this point. This, in combination with the rapid decrease of choroidal thickness and SRD, is a sign of rapid and effective treatment response with systemic and intrathecal chemotherapy.

Systemic treatment of the underlying disease is mandatory in these cases. If the ocular disease is not responsive, escalating treatment for the resistant ALL disease with other systemic therapeutic options such as immunotherapy and/or with localized radiotherapy is advised. If left untreated, leukemic ocular infiltrative disease may cause significant visual loss. Fortunately, the condition is usually very responsive to systemic treatment with chemotherapy, local radiation treatment, or a combination of both [9,10]. However, cranial irradiation has important short and long-term implications, which are especially important to consider in the pediatric population [2]. Following the St Jude total Therapy study 16, a major accomplishment has been the elimination of prophylactic cranial irradiation, previously considered the standard treatment of patients with high-risk ALL, without jeopardizing leukemia control in the CNS [11].

In our case, we observed a substantial reduction in central choroidal thickness, concurrent with the regression of the serous retinal detachment only two days after treatment was initiated. After an additional two weeks, complete resolution of the serous retinal detachment was evident. Compared to available literature this can be considered as an efficient treatment response. Bajenova et al. reported a case with near complete resolution of the SRD after 4 weeks with no specified chemotherapy [12]. In a comparable case, described by Murtaza et al., induction chemotherapy with single intrathecal chemotherapy was initiated after the diagnosis of leukemic choroidopathy. Resolution of the subretinal fluid was only seen after eight weeks [9]. In general, intrathecal chemotherapy is considered a safe treatment. However, complications can arise, with spinal cord lesions being the most important [2].

Munch et. al have shown higher concentrations in vascular endothelial growth factor (VEGF) in CSF in patients with leukemia.[13] It is possible that a higher expression of VEGF also plays a role in choroidal infiltration and SRD formation, being a possible treatment strategy in cases where resolution is not seen with systemic/ intrathecal therapy or local radiation therapy.

The good visual prognosis associated with a rapid response to treatment is encouraging. However, this may be counterbalanced by a lower survival rate in the presence of ocular involvement, emphasizing the need for a comprehensive approach to address both systemic and ocular issues [5,6].

Because of the various similarities between the eye and the brain, the eye could be of great importance in our understanding of the pathophysiology and possible treatment strategies of the disease. In several well-defined neurodegenerative conditions that effect the brain and spinal cord, ocular symptoms precede conventional diagnosis. Ophthalmic evaluation in patients with leukemia could serve as a noninvasive approach to determine the risk/ presence of central nervous system involvement [14].

4. Conclusion

SRD is a rare form of retinal/CNS involvement in children with ALL that warrants additional intrathecal chemotherapy. The ophthalmologist plays a critical role in identifying ocular involvement in leukemia at initial presentation and in assessing retinal/CNS disease remission during/after treatment. We suggest routine ophthalmological assessment in the primary screening of acute leukemia, with baseline imaging including EDI-OCT as the main diagnostic tool for diagnosis and follow-up.

Acknowledgement

The completion of this paper would not have been possible without the support and guidance of prof. dr. Ingele Casteels (University Hospitals-Leuven). I would also like to thank Prof. Dr. Julie Jacob, specialized in medical retina, for sharing her insightful feedback and expertise, and Prof. Dr. Heidi Segers and Prof. Dr. Sandra Jacobs for sharing their knowledge in the field of hemato-oncology to obtain a multidisciplinary view of the case.

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