Multimodal retinal imaging in leukemic retinopathy in children with chronic myeloid leukemia

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Abstract

Objective: To evaluate changes in multimodal retinal imaging of patients with chronic myeloid leukemia. Methods: Observational case series study. All patients underwent a complete ophthalmic examination and were imaged with multimodal imaging before and after therapy for CML. Results: Mean age at diagnosis was 15 years old. All patients were male. The retinal findings at diagnosis were foveal infiltrates in 66.6%, retinal infiltration in 66.6%, venous dilation and arterial tortuosity in 66.6%, retinal hemorrhages in 100%, pre-retinal hemorrhages 33.3%, cotton-wool spots in 66.6%, Roth’s spots in 100%. Mean follow-up was 94.6 weeks (range 20-150 weeks). Regression of LR was completed after 100 days (range 56-170 days), and regression of macular infiltrates, at day 19 (range 17-21 days). Conclusion: MRI can provide relevant information when monitoring clinical response for systemic conditions affecting the eyes. At first, foveal infiltrates tend to disappear once the induction therapy has started. Retinal hemorrhages, vascular dilation, retinal infiltrates, and cotton wool spots tend to gradually disappear associated to the reduction of mature cells into the blood stream and the achievement of a major molecular response (MMR) assessed by TR-PCR.

Keywords: leukemia, chronic myeloid leukemia, leukemic retinopathy, multimodal retinal imaging
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Abbreviations

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<tr>
<td>CML</td>
<td>Chronic myeloid leukemia</td>
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<tr>
<td>CP</td>
<td>Chronic phase</td>
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<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitors</td>
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<td>BCVA</td>
<td>Best corrected visual acuity testing</td>
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<td>UWF</td>
<td>Ultra-wide field color fundus retinography</td>
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<tr>
<td>FAF</td>
<td>Fundus autofluorescence</td>
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<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
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<tr>
<td>FA</td>
<td>Fluorescein angiography</td>
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<td>MRI</td>
<td>Multimodal retinal imaging</td>
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<td>LR</td>
<td>Leukemic retinopathy</td>
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ABSTRACT

TITLE: MULTIMODAL RETINAL IMAGING IN LEUKEMIC RETINOPATHY IN CHILDREN WITH CHRONIC MYELOID LEUKEMIA

Objective: To evaluate changes in multimodal retinal imaging of patients with chronic myeloid leukemia.

Methods: Observational case series study. All patients underwent a complete ophthalmic examination and were imaged with multimodal imaging before and after therapy for CML.

Results: Mean age at diagnosis was 15 years old. All patients were male. The retinal findings at diagnosis were foveal infiltrates in 66.6%, retinal infiltration in 66.6%, venous dilation and arterial tortuosity in 66.6%, retinal hemorrhages in 100%, pre-retinal hemorrhages 33.3%, cotton-wool spots in 66.6%, Roth’s spots in 100%. Mean follow-up was 94.6 weeks (range 20-150 weeks). Regression of LR was completed after 100 days (range 56-170 days), and regression of macular infiltrates, at day 19 (range 17-21 days).

Conclusion: MRI can provide relevant information when monitoring clinical response for systemic conditions affecting the eyes. At first, foveal infiltrates tend to disappear once the induction therapy has started. Retinal hemorrhages, vascular dilation, retinal infiltrates, and cotton wool spots tend to gradually disappear associated to the reduction of mature cells into the blood stream and the achievement of a major molecular response (MMR) assessed by TR-PCR.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the BCR-ABL oncogene and increased proliferation of the myeloid cell lines without losing their capacity to differentiate. (1)

The presence of the abnormal chromosome in cells of myeloid, megakaryocytic along with erythroid lineages pointed to the origination of the disorder in a stem cell, resulting in the activation of tyrosine kinase, allowing continued cell proliferation. (2)

During the 1960s in Philadelphia, Nowell and Hungerford (2) described a translocation of the long arm of chromosomes 9 and 22. From this moment on, this translocation is named Philadelphia chromosome. The presence of the abnormal chromosome in cells of myeloid, megakaryocytic along with erythroid lineages pointed to the origination of the disorder in a stem cell, resulting in the activation of tyrosine kinase, allowing continued cell proliferation. (3)

CML may be present at any age. It accounts for approximately 15% of adult leukemia cases, 9% in patients between the ages of 15 and 19 and 2% in children under 15. (4, 5)
CML has a triphasic clinical course: a chronic phase (CP), which is present at the time of diagnosis in approximately 85% of patients; an accelerated phase, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment; and blast crisis, a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner. (6)

The ophthalmic manifestations of leukemia can result from primary or direct leukemic infiltration of ocular tissues, or secondary or indirect ocular involvement following systemic leukemic changes. (7)

The direct leukemic infiltration can show three patterns: anterior segment uveal infiltration, orbital infiltration, and neuro-ophthalmic signs of central nervous system leukemia, which include optic nerve infiltration, cranial nerve palsies, and papilledema. The secondary changes are the result of hematological abnormalities such as anemia, thrombocytopenia, hyperviscosity, and immunosuppression. (8) Adhesion of leukemic blasts to the endothelium, leukemic blast extravasation into tissues, and local hypoxia among others have been described previously as mechanisms of tissue damage in leukocytosis. (9)

Hyperviscosity of the flowing blood is generated by the overproduction and the reduced apoptosis of mature functional blood cells. Retinal flow velocity and mean retinal arterial oxygen saturation improve after cytoreductive treatment and complete hematological remission with near-normalized or normalized peripheral blood counts. (10)

The advent of tyrosine kinase inhibitors (TKI) has dramatically changed the clinical course of CML, becoming the cornerstone therapy for CML in CP; Imatinib and second generation TKI, dasatinib and nilotinib, are all approved as first-line treatment for pediatric patients. Success rates with TKI are as high as 69%, thus improving the survival rates near normal life expectancy. (11)

We reviewed the medical records of three newly diagnosed patients with leukemic retinopathy (LR) due to CML. Multimodal Retinal imaging (MRI) was analyzed at baseline and after starting treatment with TKI.

METHODS

This observational retrospective series of cases was performed between January 2017 and December 2022 at Children’s Hospital Sant Joan de D’eu (Barcelona, Spain). The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

CML diagnosis was made based on the complete blood counts, peripheral smear cellular morphology, bone marrow aspiration, cytogenetics, and molecular studies.

All patients underwent full ophthalmologic examination, including slit lamp biomicroscopy of the anterior segment, ocular adnexa, and dilated fundus examination. Best-corrected visual acuity (BCVA) was expressed as the logarithm of the minimal angle of resolution (logMAR). Ultra-wide field color fundus retinography (UWF), fundus autofluorescence (FAF), optical coherence tomography (OCT), and fluorescein angiography (FA) were performed prior systemic treatment and during follow-up.

RESULTS

Three male patients with LR associated to CML were analyzed. Mean age at diagnosis was 15 years old. Ocular and medical histories were unremarkable in all patients.

Patient 1 was referred to the ophthalmology as per general assessment in leukemia onset. Patients 2 and 3, both claimed blurring vision at presentation. Patient 3 showed central scotoma in both eyes. Mean BCVA at the diagnosis was 0.25 (range 0.0-0.5). In all the patients pupillary reflexes were symmetric and reacted to light, anterior segment examination was unremarkable. The retinal findings at diagnosis were foveal infiltrates in two patients (4 eyes, 66.6%), retinal infiltration (4 eyes, 66.6%), venous dilation and arterial tortuosity in 4 eyes (66.6%), retinal hemorrhages (six eyes, 100%), pre-retinal hemorrhages (2 eyes, 33.3%), cotton-wool spots (4 eyes, 66.6%), Roth’s spots (6 eyes, 100%) (Figure 1). Ophthalmologic findings and clinical characteristics are summarized in Table 1 and Table 2, respectively.
Patient 1 was treated with Dasatinib, and patients 2 and 3 were treated with Imatinib. All of them received hydroxycarbamide as adjuvant cytorreduction therapy.

Mean follow-up was 94.6 weeks (range 20-150 weeks). Regression of LR was completed after 100 days (range 56-170 days), and regression of macular infiltrates, at day 19 (range 17-21 days). Regression of retinal infiltrates at the periphery left pigmentary changes at the retinal pigment epithelium (RPE) in two patients (4 eyes, 66.6%). Final visual acuity was 0.0 (logMAR) in all patients.

DISCUSSION

MRI can provide relevant information when monitoring clinical response for systemic conditions affecting the retina. At first, foveal infiltrates tend to disappear once the induction therapy has started. Retinal hemorrhages, vascular dilation, arterial tortuosity, retinal infiltrates and cotton-wool spots tend to gradually disappear associated to the reduction of mature cells into the blood stream and the achievement of a major molecular response (MMR) assessed by TR-PCR.

Two cases with dense retinal infiltration at the periphery progressed to pigmentary changes at the level of RPE after complete resolution of such lesions. Interestingly, infiltration at the macula did not develop any alterations in the RPE. We hypothesize that RPE changes are dependent on the high density of infiltrates into the retina prior to treatment.

Case reports in the literature describe retinal lesions in patients with leukemia (1, 10, 12, 13) However, our report focuses on the immediate changes on MRI with ITK and hydroxycarbamide therapy in CML and the importance of combining such images in addition to clinical response, complete blood counts, and MMR assessed by TR-PCR.

It is striking that all of our patients had retinal impairment, underscoring a high incidence of ocular involvement in CML. This report can help guide ophthalmologic follow-up in these patients and avoid other unnecessary procedures.

CONFLICT OF INTEREST STATEMENT: The authors declare no conflict of interest.

ACKNOWLEDGEMENTS: Ophthalmology service staff for performing the multimodal imaging to each patient.

REFERENCES


**Figure 1.** Multimodal retinal imaging of three patients with leukemic retinopathy.

A-B: Baseline ultra-wide field (UWF) fundus photography of case 1 showing vascular tortuosity, retinal hemorrhages, and retinal infiltrates into the retina.

C-D: Same patient after eight weeks of treatment with standard therapy for CML.

E-F: Peripheral hyper fluorescence where retinal infiltrates resolved leaving retinal pigment epithelial defects.

G-H: Optical coherence tomography (OCT) showing bilateral foveal infiltrates.

I-J: OCT showing regression of foveal infiltrates after 17 days of treatment.

K-L: UWF fundus photography of case 2 at diagnosis showing retinal infiltrates, Roth’s spots, and vascular tortuosity.

M-N: UWF fundus photography of case 2 after three weeks of treatment showing regression of retinal infiltrates; mild vitreous hemorrhage appeared in the left eye.

O-P: UWF fundus autofluorescence eight weeks after treatment showing hyper autofluorescence where retinal infiltration was observed; hypo autofluorescence was noted due to blockade generated by retinal hemorrhages.

Q-R: Case 2 baseline OCT showing foveal infiltrates.

S-T: OCT showing regression of foveal infiltrates after 21 days of treatment.

U-V: UWF fundus photography of case 3 showing retinal hemorrhages at various levels (subretinal, intra-retinal, and sub internal limiting membrane).

W-X: UWF photographs of case 3 showing resolution of retinal hemorrhages after eight weeks of treatment.
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