

# Review of Proliferative Retinopathy in Chronic Myeloid Leukemia (CML)

Alan Chew Bonilla\*, Emanuel Chew Bonilla, Paulina Bueno Zarazua and Federico Graue Wiechers

Department of Retina, Institute of Ophthalmology Fundacion Conde de Valenciana, Mexico City, Mexico

## Abstract

Proliferative retinopathy is a significant ocular complication associated with Chronic Myeloid Leukemia (CML) and other forms of leukemia. Understanding the various ophthalmological manifestations and their management is important for improving patient outcomes. This review aims to provide a comprehensive overview of the ocular alterations seen in leukemia patients, with a particular focus on proliferative retinopathy in CML, its delayed manifestation and management strategies.

A thorough literature review was conducted, emphasizing key studies and case reports that highlight the ocular complications of leukemia, particularly those related to proliferative retinopathy in CML. Leukemia can cause a range of ophthalmic manifestations, including retinal hemorrhages, microaneurysms and neovascularization. Proliferative retinopathy, characterized by abnormal neovascularization is more common in chronic leukemias like CML. This condition often presents in the advanced stages of CML and can significantly impair vision if not managed promptly. The pathogenesis involves chronic hypoxia, leukostasis and inflammatory mediators, leading to the formation of fragile new blood vessels. Delayed manifestation of proliferative retinopathy in CML underscores the importance of regular ophthalmological surveillance, even in patients with well-controlled systemic disease.

Early detection and timely intervention are essential in managing proliferative retinopathy in CML. A multidisciplinary approach involving both hematologists and ophthalmologists is essential for optimal patient care. Regular follow-up and vigilant screening for ocular changes can significantly improve the prognosis and quality of life for leukemia patients. This review highlights the need for ongoing research and education to better understand and manage the ocular complications of leukemia.

**Keywords:** Chronic myeloid leukemia • Late-onset proliferative retinopathy • Ophthalmological surveillance • Hematological malignancies • Multidisciplinary approach

## Introduction

Proliferative retinopathy is a significant ocular complication associated with various forms of leukemia, notably Chronic Myeloid Leukemia (CML) [1]. This review delves into the ophthalmological alterations observed in leukemia patients, with a focus on the proliferative retinopathy linked to CML, including its delayed manifestation, management and prognosis.

## Literature Review

### Ophthalmological alterations in leukemia

Leukemia, a malignancy of the blood-forming tissues, can present various ocular manifestations. These alterations can range from minor

visual disturbances to severe vision-threatening conditions. Common ophthalmic manifestations in leukemia include retinal hemorrhages, cotton wool spots and leukemic infiltrates. These signs are indicative of the underlying hematological disorder and necessitate prompt ophthalmological evaluation and intervention.

**Acute leukemias:** Ophthalmic manifestations are primarily due to the rapid proliferation of malignant cells, leading to leukostasis and infiltration of ocular tissues. Retinal hemorrhages and cotton wool spots are frequently observed in these patients, often correlating with the severity of the hematological disease [2]. Other potential findings include optic disc edema and vitreous hemorrhage. Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) can both present with these complications.

In AML, retinal hemorrhages and cotton wool spots are common due to the high burden of leukemic cells in the peripheral blood, which

\*Address for Correspondence: Alan Chew Bonilla, Department of Retina, Institute of Ophthalmology Fundacion Conde de Valenciana, Mexico City, Mexico; E-mail: [alanchewbonilla@gmail.com](mailto:alanchewbonilla@gmail.com)

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leads to the occlusion of the retinal vessels [3]. In ALL, similar findings can be seen, but there is also a higher propensity for optic nerve infiltration, which can cause significant vision loss if not promptly treated [4].

**Chronic leukemias:** This particularly in CML and Chronic Lymphocytic Leukemia (CLL), present a distinct set of ophthalmological challenges. The slower progression of these malignancies allows for more insidious and often initially asymptomatic ocular involvement. However, as the disease advances, significant retinal complications, such as proliferative retinopathy, can occur [5]. In CLL, ocular involvement is less common but can still occur, with retinal hemorrhages, venous stasis retinopathy and optic nerve involvement being the primary manifestations [6].

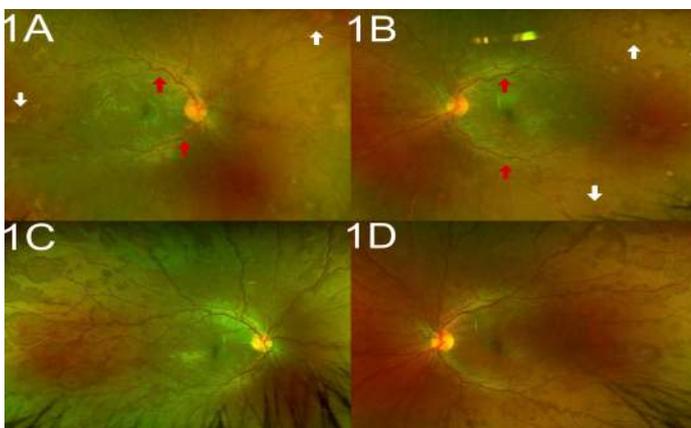
### Ophthalmological alterations in CML

CML is characterized by the presence of the Philadelphia chromosome, resulting from a translocation between chromosomes 9 and 22. This genetic anomaly leads to the uncontrolled proliferation of myeloid cells. In the context of ophthalmology, CML can cause various retinal changes, including retinal hemorrhages, microaneurysms and neovascularization [7].

**Retinal hemorrhages:** CML patients are often the result of leukemic infiltration and increased blood viscosity due to elevated white blood cell counts [8]. The hemorrhages are typically flame-shaped or dot-and-blot in appearance and can be accompanied by cotton wool spots [9].

**Microaneurysms:** These are another common finding in CML patients. These small outpouchings of the retinal capillaries can leak fluid and cause macular edema, leading to vision loss [7]. The presence of microaneurysms indicates chronic retinal ischemia and is often seen in conjunction with other signs of retinopathy.

**Retinopathy:** The most concerning ocular manifestation of CML is proliferative retinopathy. This condition is marked by the formation of new, fragile blood vessels on the retina, which can bleed and cause vision loss. Proliferative retinopathy in CML can be both a late complication arising after years of disease progression, as well as the classic leukemic retinopathy, occurring within the first manifestations of CML as shown in Figure 1 [10,11].

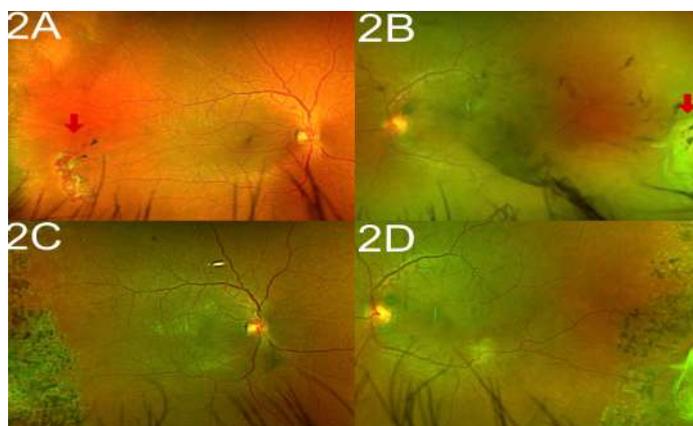


**Figure 1.** Leukemic retinopathy as the initial presentation of chronic myeloid leukemia. Note: (A,B) A 23-year-old male with no significant medical history presented with complaints of seeing black

spots. Upon examination, retinal vascular tortuosity in both eyes (red arrow) and Roth spots (white arrow) were observed, as shown in fundus photography; (C,D) These findings led to the diagnosis of chronic myeloid leukemia. The initial white blood cell count was 3,60,000/ $\mu$ l and visual acuity was normal. At the 6-week follow-up after treatment with imatinib, the vascular tortuosity and Roth spots had resolved, as demonstrated by fundus photography. The white blood cell count at that time was 5,190/ $\mu$ l, these are all shown in Figure 1.

### Proliferative retinopathy in leukemia

Proliferative retinopathy, characterized by abnormal neovascularization, can occur in various forms of leukemia. The pathogenesis involves hypoxia-induced Vascular Endothelial Growth Factor (VEGF) release, prompting the growth of new blood vessels. These vessels are prone to bleeding and can lead to vitreous hemorrhage and retinal detachment as shown in Figure 2.



**Figure 2.** Late manifestation of proliferative retinopathy secondary to chronic myeloid leukemia. **Note:** (A,B) A 52-year-old male with a 22-year history of Chronic Myeloid Leukemia (CML) initially presented with a White Blood Cell Count (WBC) of 4,02,200/ $\mu$ l, with leukocytosis persisting until 2005. Following this period, the patient remained in remission for over 15 years without any visual disturbances until 2022. At that time, the patient reported visual impairment in the left eye, prompting further evaluation. Fundus examination revealed peripheral neovascularization (red arrow) in both eyes and vitreous hemorrhage in the left eye, as depicted in fundus images; (2B) The patient underwent fluorescein angiography-guided panretinal photocoagulation targeting the ischemic retinal areas. Follow-up evaluations post-treatment showed regression of the neovascularization, as evidenced by fundus images, these are all shown in Figures 2C, 2D.

**Acute leukemias:** Proliferative retinopathy is less common but can occur due to severe retinal ischemia and VEGF overexpression [1]. Prompt treatment with anti-VEGF therapy and laser photocoagulation is often necessary to preserve vision.

**Chronic leukemias:** This particularly in CML, are more commonly associated with proliferative retinopathy. The slower progression allows for chronic hypoxia, promoting neovascularization over time. Proliferative retinopathy in CML typically presents in advanced stages of the disease [12].

## Proliferative retinopathy in CML

Proliferative retinopathy in CML is a critical complication that can significantly impact patients' quality of life. The condition is characterized by the growth of new, abnormal blood vessels on the retinal surface and into the vitreous. These vessels are fragile and can lead to recurrent vitreous hemorrhages and tractional retinal detachment [13].

Microangiopathy, as it occurs in CML, can also be found in diabetes, a usual comorbidity. While in diabetes there is a loss of pericytes, endothelial dysfunction and thickening of the basement membrane, in CML micro-angiopathy occurs due to hyperviscosity and endothelial injury mediated by toxins. It is expected that when these two diseases coexist, angiopathy will have a worse course, where proliferative retinopathy appears more quickly, as well as more intensely [14].

### Pathophysiology

The development of proliferative retinopathy in CML involves several mechanisms:

**Chronic hypoxia:** Persistent hypoxia in the retinal tissue due to inadequate blood supply triggers VEGF release, promoting neovascularization [12].

**Leukostasis:** High white blood cell counts cause sludging in the retinal vessels, leading to localized ischemia and further stimulating VEGF production [15].

**Inflammatory mediators:** Inflammation associated with leukemic infiltration can also contribute to the pathological angiogenesis observed in proliferative retinopathy.

### Clinical features

Patients with proliferative retinopathy due to CML may present with:

- Decreased vision
- Floaters
- Photopsia (flashes of light)
- Visual field defects

### Diagnosis

The diagnosis of proliferative retinopathy in CML involves a comprehensive ophthalmological examination, including:

**Fundus photography:** To document retinal changes and monitor progression.

**Fluorescein angiography:** To assess retinal blood flow and identify areas of neovascularization and leakage [15].

**Optical Coherence Tomography (OCT):** To visualize retinal thickness and structural changes.

## Management

Management of proliferative retinopathy in CML requires a multidisciplinary approach:

**Medical management:** Systemic control of CML with Tyrosine Kinase Inhibitors (TKIs) such as imatinib, dasatinib or nilotinib is important to reduce leukemic burden and prevent ocular complications [16].

**Ophthalmic interventions:** Anti-VEGF injections and laser photocoagulation are mainstays of treatment for proliferative retinopathy. Vitrectomy may be necessary in cases of non-resolving vitreous hemorrhage or retinal detachment [14].

### Delayed manifestation of proliferative retinopathy in CML

Delayed manifestation of proliferative retinopathy in CML is a notable concern. Even with effective systemic treatment, ocular complications can arise years after the initial diagnosis. This delayed onset underscores the importance of regular ophthalmological surveillance in CML patients.

### Case reports and studies

Several studies and case reports highlight the delayed presentation of proliferative retinopathy in CML. For instance, Chew et al. reported a case where a patient was discovered with significant retinal neovascularization years after achieving hematological remission [17]. These findings emphasize the need for ongoing vigilance and timely referral to ophthalmologists.

In a case reported by Brown et al., a young adult with CML presented with bilateral vision loss as the initial symptom. Despite effective systemic treatment, the patient developed proliferative retinopathy, highlighting the importance of regular ophthalmological follow-up even in the absence of initial ocular symptoms [13].

There are also case reports where proliferative retinopathy is the first expression of CML. Quidi et al., describe the case of a 32-year-old woman who presented with visual impairment in both visual fields. On ophthalmologic examination, bilateral proliferative retinopathy was found. Photocoagulation and vitrectomy were suggested and preoperative studies revealed hyperleukocytosis. Genetic tests were subsequently performed to confirm CML [18].

Macedo et al., report the case of a 48-year-old man who sought medical attention due to recent loss of visual acuity and floaters in both eyes [19,20]. Fundoscopy revealed bilateral peripheral neovascularization and subsequently confirmed by fluorescein angiography (peripheral capillary dropout angiography) (Table 1). Laboratory studies showed hyperleukocytosis among other hematologic manifestations. The diagnosis of CML was confirmed following that [10].

**Table 1.** Clinical characteristics, leukocyte counts and treatments for CML-Associated Proliferative Retinopathy.

Author, year	Patient's age, sex	Leukocyte count at diagnosis of retinopathy	Detection of Proliferative Retinopathy After Leukemia diagnosis	Ophthalmologic interventions	Leukemia treatment
Morse et al. [19]	32 years, Male	No information	2 years (delayed manifestation)	No information	Busulfan
Frank et al. [7]	30 years, Male	2,50,000/ $\mu$ l	4 years (delayed manifestation)	Photocoagulation	Busulfan (untreated a year before diagnosis of retinopathy)
Nobacht et al. [8]	23 years, Female	4,400/ $\mu$ l	2 years (delayed manifestation)	Photocoagulation	Hydroxy-ureum and a bone marrow transplant
Huynh et al. [20]	46 years, Male	No information	Recent diagnosis	Photocoagulation	Imatinib
Macedo et al. [10]	48 years, Male	2,48,000/ $\mu$ l	Undiagnosed CML	Photocoagulation and vitrectomy	Imatinib
Almeida et al. [21]	46 years, Male	2,43,900/ $\mu$ l	Undiagnosed CML	Photocoagulation and vitrectomy	Dasatinib
Priya et al. [12]	58 years, Male	2,085,000/ $\mu$ l	Undiagnosed CML	Photocoagulation	Imatinib
Quiddi et al. [18]	32 years, Female	1,65,000/ $\mu$ l	Undiagnosed CML	Photocoagulation and vitrectomy	Imatinib
Brown et al. [13]	28 years, Male	2,58,000/ $\mu$ l	Undiagnosed CML	Intravitreal injections of Bevacizumab	Dasatinib
Chew et al. [17]	52 years, Male	10,460/ $\mu$ l	21 years (delayed manifestation)	Photocoagulation	Nilotinib

## Referral to ophthalmologists

Given the potential for severe ocular complications, it is imperative to refer leukemia patients to ophthalmologists at the time of diagnosis. Early referral allows for baseline ocular examination and timely detection of any retinal changes [21].

## Follow-up protocols

Regular follow-up with ophthalmologists should be integrated into the management plan for leukemia patients. Suggested follow-up intervals include:

**Initial diagnosis:** Comprehensive eye exam to establish baseline retinal health.

**During treatment:** Regular monitoring every 3-6 months, depending on the patient's clinical status and response to therapy.

**Post-treatment:** Annual examinations to detect late-onset complications [11].

## Prognosis and ophthalmological involvement

The prognosis of leukemia patients with ocular involvement varies based on the severity of retinal changes and the effectiveness of systemic and ocular treatments. Proliferative retinopathy, if left untreated, can lead to irreversible vision loss. However, with timely intervention, the prognosis for visual outcomes can be significantly improved.

Patients with well-controlled CML who receive appropriate ophthalmological care can maintain good vision and quality of life. The integration of ophthalmological monitoring into the overall management plan for CML patients is important for achieving optimal outcomes.

## Recommendations for ophthalmologists

Ophthalmologists play a significant role in the multidisciplinary care of leukemia patients. Key recommendations include:

**Early detection:** Vigilant screening for retinal changes in newly diagnosed leukemia patients.

**Collaborative care:** Working closely with hematologists to coordinate care and manage ocular complications.

**Patient education:** Informing patients about the potential ocular risks and the importance of regular eye examinations.

Ophthalmologists should be aware of the specific ocular complications associated with different types of leukemia and tailor their screening and treatment protocols accordingly. In CML, the focus should be on early detection and management of proliferative retinopathy to prevent vision loss.

## Conclusion

Proliferative retinopathy is a severe ocular complication associated with CML and other forms of leukemia. Understanding the pathophysiology, clinical features and management strategies of this condition is essential for improving patient outcomes. Regular ophthalmological follow-up and a collaborative approach between hematologists and ophthalmologists are critical in managing these patients effectively. Early detection and timely intervention can significantly enhance the prognosis and quality of life for leukemia patients with ocular involvement.

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