Chapter

Clinical and Imaging Features of Leukemic Retinopathy

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Abstract

Hematological malignancies may be associated with ocular manifestations in up to 50% of cases, and ocular symptoms can be the initial presentation. Retinal leukemic infiltrates may be observed in up to 3% of leukemia patients. Leukemic retinopathy may present more commonly in acute leukemias than chronic leukemias as Roth's spot, multi-level retinal hemorrhages, cotton wool spots, or opportunistic infection secondary to pancytopenia. On the other hand, patients with chronic leukemias, such as chronic myeloid leukemia (CML), may present with leukemic retinal infiltrates and venous stasis secondary to hyperviscosity, which may lead to secondary peripheral microaneurysms and neovascularization. Vascular complication, such as central retinal vein occlusion, may also occur as a result of venous stasis. In addition, leukemic retinopathy is associated with poorer overall survival as pediatric CML patients without ocular manifestation may have twice as high 5-years survival rate compared with those with ocular manifestation. The presence of leukemic retinopathy is associated with more severe systemic disease and is correlated with hematological parameters such as white blood cells count (WBC). In addition, a positive correlation was found between ocular leukemic infiltration and agonal leukocyte count and the severity of systemic disease in an autopsy study. Therefore, the presence of retinal infiltrate may be associated with leukemia with extreme leukocytosis. Optical Coherence Tomography (OCT) is a noninvasive retinal imaging tool that can help diagnose leukemic retinopathy. Inner retina hyper-reflective lesions were observed in areas with intra-retinal hemorrhages or hemorrhagic lesions, while outer retina hyper-reflective lesions were observed in areas with whitish retinal infiltrates. In addition, the loss of the physiological hourglass appearance on cross-sectional OCT scan of retinal vessels may be seen in leukemic retinopathy. It is believed that intraluminal blood flow is responsible for the physiological hourglass appearance, consisting of two paired hyper-reflectivities inside vessel wall on OCT. In leukemic retinopathy, hyperviscosity may disrupt normal intraluminal blood flow, leading to the loss of this physiological appearance. In summary, leukemic retinopathy can be the first presentation of leukemia. Ophthalmologists can play an important role in the diagnosis of leukemia. Noninvasive retinal imaging could help us to monitor and understand the pathophysiology of leukemic retinal infiltrates. Prompt diagnosis and treatment of underlying leukemia may preserve vision and prolong survival rate.

Keywords: leukemia, leukemic retinopathy, leukemic infiltrate, ocular manifestations, retinal hemorrhage

1. Introduction

Leukemia is a neoplastic disorder caused by abnormal proliferation of hematopoietic stem cells that replace the normal bone marrow. Although patients typically present with fatigue, bleeding, and fever, ocular manifestations have been reported to occur in up to 50% of cases at the time of diagnosis [1]. It is vital to assess for ocular symptoms, which may possibly be the first and isolated indicator for disease occurrence, relapse, or progression [2].

Leukemia can either arise from the myeloid or lymphoid cells lines. They can be rapidly progressing (acute) or indolent (chronic). Acute leukemia is fast progressing, generating immature white blood cells (WBC) incapable of normal physiological function, which can lead to imminent death without prompt treatment. Chronic leukemia progresses gradually with higher proportion of mature cells, although they can transform into an aggressive phase. The four major types of leukemia include acute myeloid leukemia (AML), most commonly seen in older adults, chronic myeloid leukemia (CML), with a progressive clinical course, acute lymphoblastic leukemia (ALL), most commonly seen in children with fair survival rate, and chronic lymphocytic leukemia (CLL), a slowly progressing disease with better prognosis. Both acute and chronic leukemia can cause ocular complications, while retina is the most common ocular tissue to be involved.

Patients with leukemic retinopathy may experience a more aggressive course and worse overall disease outcome. Studies have shown a significantly shorter mean survival rate in leukemic patients with leukemic retinopathy compared with those without (21.4% vs. 45.7) [3, 4]. It has also been shown that among patients with leukemic retinopathy, the mean survival rate was significantly shorter in those with cotton wool spots than those without [5]. Hematological parameters such as raised WBC and a low platelet count have been shown to correlate with retinal changes in leukemic patients [6]. Raised WBC has also shown to be positively correlated with the presence of leukemic retinal infiltrates and overall survival rate [7].

2. Pathogenesis

Ocular involvement in leukemia can be divided into: 1) primary (or direct) leukemic infiltration of ocular structures by neoplastic cells, and 2) secondary (or indirect) involvement due to hematological abnormalities (anemia, thrombocytopenia and hyperviscosity), central nervous system (CNS) involvement, opportunistic infection, or treatment-related complication. The term leukemic retinopathy is used to describe the retinal manifestation secondary to hematological abnormalities rather than direct leukemic infiltration [8].

Primary infiltration of neoplastic cells can occur virtually in all ocular tissues including the retina (3%), orbit (1%), choroid (0.3%), and optic nerve (0.3%) [6]. Direct infiltration of the retina occurs across all levels, more commonly in the inner retinal layers [9, 10]. These aggregates of leukemic cells in the retina can cause complete or partial structural destruction [8]. Generally, the internal limiting membrane (ILM) acts as an effective barrier against leukemic cells infiltration, but occasionally invasion into the vitreous can occur [11]. Invasion of leukemic cells into the choroid reduces blood flow in choriocapillaries and alters

the retinal pigment epithelium (RPE), which in turn result in an accumulation of subretinal fluid and serous retinal detachment. Choroidal mass may be evident. Optic nerve involvement may be caused by direct infiltration of optic nerve head, passive swelling due to retrolaminar leukemic infiltration, or passive swelling in papilloedema [6].

Secondary or indirect ocular involvement has been described in up to 39% of leukemic patients [1]. Hematological abnormalities including anemia, thrombocytopenia lead to retinal hemorrhage at all levels, which may be accompanied by white-centered retinal hemorrhage and perivascular sheathing due to accumulation of leukemic cells [12]. Hyperviscosity due to elevated WBC results in vascular stasis and occlusion [12, 13]. Prolonged vascular stagnation especially in chronic leukemia may lead to peripheral retinal ischemia and eventually blinding complications such as proliferative retinopathy or even neovascular glaucoma [14, 15].

3. Clinical presentation

3.1 History

Ocular symptoms: Most patients are asymptomatic. Some may experience unilateral or bilateral blurring of vision, floaters, or visual field defect. Ocular manifestations are more common in acute or relapse phase of leukemia than in chronic leukemia [16].

Systemic symptoms: Acute leukemia presents with symptoms of anemia, hemorrhage, infection, or infiltration of lymphatic organs. On the other hand, symptoms of chronic leukemia are vague, such as fatigue, weight loss, and night sweats. Patients with hyperviscosity syndrome may have headache, hearing impairment, dizziness, and other neurological symptoms.

The review of past history including any past history of leukemia or malignancies, systemic illness, history of infection, any previous treatments received is important in aiding diagnosis of leukemic retinopathy.

4. Physical examination

4.1 Ocular features

Retinal changes can be related to primary leukemic infiltration or secondary retinal manifestations of hematological abnormalities. Secondary changes occur in leukemic retinopathy, including Roth's spot, multi-level retinal hemorrhages, cotton wool spots, and opportunistic infection. These findings present more commonly in acute leukemia [1]. Chronic leukemia develops less rapidly, in which prolonged hyperviscosity results in venous stasis, retinal ischemia, peripheral microaneurysms, and proliferative vitreoretinopathy [1]. Complications such as vascular occlusion, vitreous hemorrhage, neovascular glaucoma, tractional retinal detachment secondary to proliferative vitreoretinopathy may develop in untreated eyes or delayed presentation. These manifestations vary in severity, which can be classified into mild, moderate, and advanced disease depending on the region involved and by visual prognosis (**Table 1**) [17].

	Categorization of ophthalmic manifestations in CML patients
Mild	• Retinal hemorrhages, Roth spots, cotton wool spots, leukemic infiltrates, dilated tortuous vessels, optic disc hyperemia and edema, retinal vessels sheathing
Moderate	• Proliferative retinopathy
	• Retinal vein occlusion
	• Vitreous hemorrhage
Advanced	• Optic disc infiltration
	• Exudative retinal detachment
	• Choroidal infiltration and hemorrhage

Table 1.
Categorization of ophthalmic manifestations in CML patients [17].

a. Venous dilatation and tortuosity

- Vascular congestion is one of the earliest retinal manifestations. It is also the most common manifestation in chronic leukemia [12]

b. Multi-level retinal hemorrhages

- Retinal hemorrhages occur predominantly in the posterior pole
- All retinal layers, especially the inner layers may be involved
    - Preretinal hemorrhages, superficial flame-shaped hemorrhages, intraretinal dot blot hemorrhages, sub-ILM hemorrhages, subhyaloid hemorrhage, and vitreous hemorrhage
- White-centered hemorrhage or Roth's spots result from capillary rupture and extrusion of whole blood, while the white center consists of leukemic cells or platelet-fibrin aggregates [13]
- There is an inconsistent correlation between retinal hemorrhages and hemoglobin or platelet levels [8]

c. Perivascular sheathing

- Perivascular sheathings are gray-white streaks along retinal vessels, which are a collection of leukemic cells [8]

d. Cotton wool spots (CWS)

- CWS is not a unique feature for leukemic retinopathy but is also seen in other pathologies with retinal hypoxia. They are a collection of neuronal debris within nerve fiber layer due to ischemic disruption of nerve axons
- Hypoxic state in leukemic retinopathy results from vascular stagnation and occlusion

- The presence of CWS does not correlate with hematological parameters [18]

e. Microaneurysms (MA)

- MA is a less common manifestation, which tends to locate in the peripheral retina in chronic leukemia. It is considered a manifestation of ischemia and neovascularization secondary to raised WBC [8, 19]

- There is no correlation between the presence of MA and hemoglobin or platelet count [20]

f. Leukemic infiltrates

- Leukemic infiltrates can occur in all ocular tissues, with retina being the most common site of involvement

  - Retinal infiltrates are large gray, white nodules of varying size that can involve all levels of retina, especially common in outer retinal layers. Subretinal infiltrates have been referred as subretinal hypopyon

  - Smaller infiltrates tend to be perivascular, while massive retinal infiltrate can cause total retinal detachment [21]

  - Massive retinal infiltrates may appear as large confluent retinal infiltrates in CML patients with extreme leukocytosis [9, 10].

  - Histological examination demonstrates complete or partial focal tissue destruction with the invasion of retinal infiltrates [8]. However, complete resolution with functional recovery may occur with systemic treatment [22]

  - Other sites of leukemic infiltration including the choroid, vitreous, and the fovea are less frequently seen. Choroidal infiltration often presents as secondary serous retinal detachment, generally shallow at the posterior pole [1]

- Direct leukemic infiltrates correlate positively with increased WBC and severity of systemic disease [7]

g. Optic disc swelling

- Optic disc swelling may occur in direct optic nerve head infiltration, passive swelling due to retrolaminar leukemic infiltration, or passive swelling in papilloedema [6]

- Clinically, papilledema and direct optic nerve head infiltration may be differentiated by the presence of perivascular sheathing in the later, although occasionally the conditions overlap [8]

- Optic nerve dysfunction (drop in visual acuity, color vision deficit, and the presence of relative afferent pupillary defect) may occur when the retrolaminar portion of the optic nerve is involved

- Lumbar puncture and spinal fluid analysis provides information on CNS involvement or raised intracranial pressure but cannot exclude direct optic nerve head infiltration

h.Complications

- Retinal vein occlusion
  - Retinal vein occlusion occurs as a result of hyperviscosity due to leukocytosis [1]
- Serous or exudative retinal detachment
  - This is thought to be a result of choroidal infiltration of leukemic cells or RPE disruption
  - Only a few cases of serous retinal detachment have been reported. Most of the reported cases are of ALL in younger patients. The detachments are generally shallow over the posterior pole
- Proliferative retinopathy
  - Proliferative retinopathy occurs secondary to retinal ischemia in non-perfused retina due to hyperviscosity
  - Peripheral retinal neovascularization is frequent in chronic leukemia, observed in up to 78% of cases in CML [19].On the other hand, optic disc neovascularization is almost always associated with acute leukemia [23, 24]
  - In untreated eyes, vitreomacular traction, vitreous hemorrhage, and tractional retinal detachment eventually occur [22]
  - Neovascular glaucoma (NVG) and severe loss of vision may occur. The risk of developing NVG may be higher in patients with preexisting diabetic retinopathy [15, 25].

5. Investigation

5.1 Ocular imaging

Optical Coherence Tomography (OCT) is a noninvasive retinal imaging tool that uses low-coherence light waves to capture cross-sectional images of the retina. Lesions across each layer such as retinal infiltration, hemorrhages, and vessels can be visualized. Retinal and choroidal thickness can also be measured. OCT provides a detailed assessment of the structural change in the retina, which is valuable in disease monitoring. For example, the degree and extent of macular edema and serous retinal detachment can be demonstrated if not evident clinically [26]. The resolution of

leukemic infiltrates can also be observed with systemic treatment [9, 27]. The features of leukemic ocular manifestations are described further below:

a. Retinal detachment

- Separation of neurosensory retina from the underlying retinal pigment epithelium (RPE) can be confirmed on OCT, there would be a hypo-reflective space underneath the neurosensory retina

b. Retinal hemorrhages and leukemic infiltrates

- Retinal hemorrhages may present as inner retinal hyper-reflective lesions
- Leukemic infiltrates may appear as outer retinal hyper-reflective lesions, which may invade across retinal layers
- Disruption of photoreceptor layers may be observed after resolution of leukemic infiltrates [9]

c. Macular edema

- Increased central macular thickness (CMT) occurs in macular edema secondary to retinal vein occlusion
- Intraretinal cysts, subretinal fluid, and diffuse thickening may be present

d. Choroidal infiltration

- Increased choroidal thickness due to choroidal infiltration

e. Appearance of retinal vessels cross-section

- Loss of physiological hour-glass appearance over retinal vessels [28]
    - Physiological intraluminal blood flow appears as hourglass-shaped, consisting of two paired hyper-reflectivities inside vessel wall on OCT
    - Venous stasis in leukemic retinopathy disrupts normal intraluminal blood flow, leading to loss of this physiological appearance

Fundus Fluorescein Angiography (FFA) is an imaging technique to demonstrate retinal vasculature with the use of intravenous sodium fluorescein and a specialized camera. Real-time vascular flow with transit time can be recorded, together with the visualization of retinal microvasculature such as microaneurysms, capillary non-perfusion, and neovascularization, all of which may occur in leukemic retinopathy. With the advancement of ultra-widefield FFA in recent years, pathologies in the peripheral retina can be visualized. FFA is usually performed in eyes with delayed presentation, or in cases with high risk of ischemia and proliferative retinopathy due to prolonged vascular stagnation.

FFA features in leukemic retinopathy:

- Microaneurysms (MA)
    - Leukemic retinopathy may share common clinical features with diabetic retinopathy. MAs in leukemic retinopathy are smaller in size, clustered more closely to give a firecracker-appearance on FFA [29]. This picture of miliary MAs can differentiate leukemic retinopathy from a variety of ocular conditions such as Behcets retinal vasculitis, sarcoidosis where MA is not a typical feature.
- Capillary dropout representing areas of non-perfused retina
- Neovascularization at the disc (NVD) and elsewhere (NVE) secondary to retinal ischemia
- Delayed retinal arteriovenous transit time due to vascular stagnation
- Fluorescein leakage and pooling in exudative or serous retinal detachment

Optical Coherence Tomography Angiography (OCT-A) is an emerging noninvasive imaging technique, which generates angiographic images of the retina and the choroid without the need for dye injection. This imaging technique detects laser light reflectance upon moving red blood cells. Apart from structural mapping, the rate of blood flow can also be determined by scanning the same area twice for signal difference. Pathology on OCT-A can be detected even in patients without clinical signs of leukemic retinopathy. Pathological vascular flow loss in the superficial and deep capillary plexus and decrease of vascular density over perifoveal area can be detected with OCT-A in chronic leukemic patients. Currently, there are limited studies on OCT-A features in leukemic retinopathy [30].

6. Systemic investigation

Review of systemic illness should be carried out promptly to facilitate early disease diagnosis, disease staging, and to exclude concurrent infection or other differential diagnosis. The diagnosis of leukemia requires complete blood count with differential, peripheral blood smear, bone marrow examination, histochemical studies, cytogenetic and molecular testing, and immunophenotyping.

- Complete blood count and peripheral blood smear
    - Severe pancytopenia and peripheral blast cells suggest acute leukemia. Leukocytosis in the presence of blast cells excludes infection
    - Elevated white cell count and a normal-to-moderately elevated platelet count may be present in chronic leukemias. Peripheral smear and peripheral blood flow cytometry can further classify types of leukemia
    - Elevated white cell count correlates with the presence of direct leukemic infiltrates and the severity of systemic disease [7]

- Histochemical studies, cytogenetics, and immunophenotyping or molecular studies classify leukemia and provide information on disease prognosis

- Other laboratory abnormalities in leukemia may include hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, elevated lactate dehydrogenase (LDH), which may indicate a tumor lysis syndrome

- Specific tests are useful in excluding infectious or non-infectious diseases, which mimic leukemic retinopathy

    - C-reactive protein

    - Quantiferon test, purified protein derivative skin test

    - Syphilis serology, HIV test

    - Angiotensin-converting enzyme level, urinary and blood calcium levels

- Imaging

    - Chest X-ray

    - Cranial imaging is done in leukemic patients with CNS symptoms. Cranial and orbital MRI can reveal intracranial lesions, presence of mass effect, presence of orbital involvement, or optic nerve infiltration

7. Management

Close collaboration between hematology-oncology and ophthalmology team is essential for a proper management of leukemic retinopathy. The mainstay of management is to treat underlying leukemia with chemotherapy, targeted therapy, radiotherapy, immunotherapy, or hematopietic stem cell transplant depending on the type and phase of leukemia. Acute general management includes correction of metabolic, infectious, and hyperleukocytosis emergencies. Emergency medical cytoreduction treatment or even therapeutic leukapheresis may be required in cases with extreme leukocytosis.

Regular ophthalmological review with dilated fundal examination is needed to monitor for the development of complication such as proliferative retinopathy and retinal detachment.

The subsequent ophthalmological management depends on disease severity (**Table 1**). In most mild cases, symptoms improved with systemic treatment for underlying leukemia. In moderate and advance cases, ophthalmic treatment together with systemic treatment may be necessary to minimize visual damage.

- In proliferative retinopathy, panretinal laser photocoagulation is applied to reduce ischemic drive from the non-perfused retina

- Non-resolving vitreous hemorrhage, massive subretinal hemorrhage, or tractional retinal detachment may require surgical management with pars plana vitrectomy

- Macular edema secondary to retinal vein occlusion may be treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF)

8. Conclusion

Leukemic retinopathy can be the first presentation of leukemia, which warrants urgent evaluation and early commencement of systemic therapy. Clinical features vary in form and severity, in which milder forms give better visual prognosis. Retinal imaging helps us to understand the pathophysiology of leukemic retinopathy as well as to monitor disease progress. Prompt diagnosis and treatment of underlying leukemia may preserve vision and prolong survival rate.

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