Review Article

Ophthalmic Manifestations of Leukemia and Their Management

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ABSTRACT

Patients with leukemia often have ophthalmic manifestations. These occur either from direct infiltrations of neoplastic cells or from indirect or secondary causes. Nearly all ocular structures can be affected by leukemia. Sometimes, ophthalmic involvement can be the first sign of disease relapse. This review article aims to highlight different ocular manifestations of leukemia along with treatment. It involves studying the available material in textbooks, printed and online journals. As there is high prevalence of ocular findings in leukemia, it can be a standard practice that all leukemic patients should have screening by ocular examination. Awareness of the clinical spectrum of leukemic infiltration of ocular region is essential for rapid diagnosis, prompt initiation of treatment and better outcome. If prompt diagnosis and treatment can be done, worsening of vision may be minimized or prevented.

Keywords: *Leukemia, ophthalmic manifestations, leukemic infiltrate*

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INTRODUCTION

Leukemias are a category of malignant neoplasm originated in the hematopoietic stem cells due to proliferation of blood cells in the bone marrow.[1] Leukemia is categorized according to the mode of presentation, i.e., acute or chronic and the predominant proliferating cell type. Consequently, the diagnosis of leukemia will be either acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), as well as other types of leukemia.[2] Generally maturity of the WBCs, their morphology, cyto-chemical findings, and immune phenotype are used to classify the type of leukemia.[3]

Leukemic infiltration of the orbit is considered rare. If prompt diagnosis and treatment can be done, worsening of vision may be minimized or prevented. Ocular symptoms can present after the systemic diagnosis, they can be existing signs of the disease or they can be the first expression of a relapse after remission.[4,5] Ophthalmic involvement by leukemia is divided into two major categories: "primary" or direct infiltration of neoplastic cells(leukemic infiltration and white-centered retinal hemorrhages), and "secondary" or indirect involvement from nonviable or dysplastic cells, or from chemotherapy leading to hematological alterations and immunosuppression causing opportunistic infections.[6] Direct leukemic infiltration may have the following paradigms:

I) Direct infiltration of the anterior segment, vitreous, choroid, iris, ciliary body and retina resembling uveitis, choroiditis and retinitis.

II) Infiltration of the optic nerve presenting with or without another cranial nerve involvement

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(cranial nerves III, IV or VI) clinically resembling palsies and swollen disks.

III) Infiltration of the orbit resembling orbital inflammatory diseases. Intraocular leukemic involvement most commonly presents in the posterior segment. Leukemic manifestations frequently have diminished vision, pain and reduced mobility of the eye. Hemorrhages in the retina are the most common feature of leukemia.[7] Some forms of hemorrhages occur due to leukemic cell infiltration whereas other forms of hemorrhages in leu kemic patients are secondary to the systemic conditions. Secondary hemorrhages mimicking as dots or blots, flame-shaped etc. Additionally, the hemorrhage may spread into the sub retinal or vitreous spaces. Cotton wool spots in leukemic patients may be attributed to nerve fiber layer infarcts or to localized collections of leukemic cells. Peripheral micro aneurysms and peripheral neovascularization are also ocular signs of chronic leukemia.[8] Leukemia with ophthalmic manifestations are rarely examined extensively and hardly ever biopsied.

The contemporary treatment of patients with ophthalmic leukemia includes systemic chemotherapy (although it may not be adequate due to insufficient penetration of systemic chemotherapy to the involved ocular structure) and biological treatments.[9,10] Irradiation is another treatment option (Although it commonly produces local complications). Hence, treatments with intravitreal injections of dexamethasone[11], anti–vascular endothelial growth factor (anti-VEGF)[12] or methotrexate (MTX)[13] have been recently considered.

This review aims to outline the ocular manifestations and outcomes of patients with ocular leukemia. Awareness of the clinical spectrum of leukemic lesion of ocular region is essential for rapidly establishing the accurate diagnosis and start immediate treatment.

OPHTHALMIC MENIFESTATIONS

Retinal involvement: Retina is the most common site of ocular manifestations. Leukemic retinopathy is noticed in both the acute and chronic leukemia, more frequently in acute form.[14] Retinal vascular irregularity is due to hyper viscosity resulting from increased number of circulating leukocytes or platelets. The hyper viscosity leads to diminishing blood flow and vascular stasis which then give rise to peripheral retinal capillary dropout, microaneurysm formation and proliferative retinopathy. The classic feature of retinopathy includes retinal venous dilatation and tortuosity.[15] The dilatation may be irregular in diameter. Retinal vascular sheathing is frequently present. In the sheathing there are perivascular infiltration by leukemic cells. Hard exudates and cotton wool spots may also be seen. The most prominent finding is retinal hemorrhage, more frequently noticed in the posterior pole. The hemorrhages are usually red or flame-shaped confined to retina. Rarely boat-shaped hemorrhage in the sub hyaloid space extends up to vitreous, leading to obvious obscuration of visualization of the posterior pole. The intraretinal hemorrhage may contain white dots in the center which represent cellular debris, capillary emboli or accumulation of leukemic cells.[16]

Retinal infiltrate: In patients with chronic myelogenous leukemia large grayish-white nodular retinal infiltrates are found which may be associated with local destruction, necrosis, and hemorrhage. Histopathological examination reveals that internal limiting membranes are well preserved without spreading into the vitreous cavity. These nodular retinal infiltrates are noticed in association with increased leucocyte counts with major proportion of blast cells.[17] When they are associated with increased leucocytes count, it is a dangerous prognostic sign.[17]

Retinal microaneurysm and neovascularization: Several studies demonstrated that retinal micro aneurisms with occasional capillary dropout are more commonly found in patients having chronic myelogenous leukemia.[18,19] They observed that prolonged leukocytosis is an obligatory factor in the development of peripheral retinal micro aneurysm. But they were unable to find any association between duration of the disease and retinal vascular abnormality. Although in some case reports no correlation was observed between micro aneurysm formation and hematocrit level, significant correlation was noticed between retinal neovascularization and increased number of circulating platelets.[20]

Orbit and eye lid involvement: Around 2-6% of the orbital tumors of childhood are considered due to leukemia.[21] A recent study has demonstrated that about 11% of children presented with unilateral proptosis having some form of acute leukemia.[22]

There is increase prevalence of orbital involvement in leukemia due to soft tissue infiltration by leukemic cells or due to hemorrhage. Infiltration of the eye lid, orbit, or lacrimal gland may also be noticed. When retrobulbar hemorrhage occurs, it may extend forward into the subconjunctival space. Hemorrhage into the lids is also not an uncommon finding. Granulocytic sarcoma involving orbit is a typical feature of myelogenous leukemia. It may occur at any time of development of myelogenous leukemia and sometimes even before the appearance of systemic involvement. Due to diffuse orbital involvement the patient may present with proptosis following discrete orbital growth.[22]

Optic nerve infiltrates: Leukemic infiltration of the optic nerve has been considered that the disease progress to the point of involvement of the central nervous system (CNS), which is more commonly observed in acute compared with chronic leukemia, children compared with elderly people and acute lymphoblastic leukemia (ALL) compared with acute myelogenous leukemia (AML).[23] The optic nerve can be bulged from increased intracranial pressure, retro laminar leukemic invasion or by direct infiltration of the optic nerve head.[24] Retinal perivascular infiltration is the differentiating point between direct optic nerve head infiltration and papilledema. Vision is more likely to be maintained in direct infiltration of the optic nerve head compared with retro laminar involvement of the optic nerve.[25]

Anterior segment involvement: The anterior segment is rarely involved by leukemic infiltration. Comma-shaped venous irregularities of the conjunctiva have been noticed, possibly due to hyper viscosity.[26] Conjunctival tumors result in subconjunctival protrusion in AML or ALL.[27] Iris involvement is characterized by color change and a gray or yellow pseudohypopyon.[28] Due to involvement of trabecular meshwork the intraocular pressure is likely to increase.[28]

Vitreous leukemic infiltration: Despite the internal limiting membrane predominantly acts as barrier to leukemic cell infiltration, cells can infiltrate the vitreous from optic disc neovascularization and vitreous hemorrhage can permit neoplastic cells to infiltrate the vitreous cavity.[29,30]

Choroid leukemic infiltration: Although the ophthalmologic changes are not predominantly found, the choroid infiltration with leukemic cells is frequently found in histopathological examination.[31] Kincaid et al. have noticed bilateral serous detachment of the retina with diffuse infiltration of the choroid by leukemic cells.[32] Furthermore, large choroid masses with chronic myelogenous leukemia and overlying serous retinal detachment have also been observed in adults.[32] Fluorescein angiographic examinations in patients with choroidal infiltration and overlying serous detachment of the retina show innumerable retinal pigment epithelial leakage points in the early phase of the angiogram. With time these leakage points become more diffuse, and dye is found to leak into the sub retinal space.[32]

Unusual ocular manifestations in leukemia: The ophthalmologist should be aware of the unusual and diverse ophthalmological disorders in which leukemia can be presented to them. At the initial stage, leukemic process can be found as redness and swelling of the lower palpebral conjunctiva (in acute lymphocytic leukemia),[33] corneal ring ulcer (in acute monocytic leukemia),[34] Sjogren's syndrome with lacrimal gland enlargement (in chronic lymphocytic leukemia),[35] anterior segment ischemia (in chronic myelogenous leukemia),[36] open-angle glaucoma considered to be due leukemic infiltration of the trabecular meshwork (in both chronic lymphocytic leukemia and chronic myelogenous leukemia),[37,38] and finally, acute leukemic infiltration of the vitreous in a patient with acute lymphocytic leukemia.[39]

SYSTEMIC EVALUATION BY THE OPHTHALMOLOGISTS

When leukemia is suspected, the principal test is complete blood count with platelet count. If it reveals markedly elevated or decreased WBC count, the ophthalmologist should consult hematologist or oncologist. In acute leukemia, at least 20% or more blast cells are seen.[41] It is a medical emergency and patients should be immediately referred. Sometimes, extraocular deviations are visible. However, if the CBC with platelet parameter reveals no blast, lymphocyte predominance with mature appearing cells and basophilia, findings indicate chronic leukemia.[41] These patients should be referred to consult with hematologist/oncologist within 1-2 weeks.

TREATMENT

We must be aware of the basis of our management in such cases, that is to treat the underlying malignancy.

In Acute lymphoblastic leukemia: The prognosis for a patient having acute lymphoblastic leukemia mainly depends on the underlying cytogenetic and molecular characteristics. In the induction phase chemotherapeutics minimize the tumor burden by clearing leukemic cells in the bone marrow. Acute lymphoblastic leukemia tends to infiltrate the CNS. Therefore, intrathecal prophylaxis is judgmental. In the consolidation phase, the target is to eliminate any leukemic cells which remain viable. In the maintenance phase, chemotherapeutics and steroids are considered in combination to prevent recurrence. In unfavorable acute lymphoblastic leukemia, allogeneic stem cell transplantation may be considered. However, immediate radiotherapy administration to the eye, combined with systemic chemotherapy, may be useful in preservation of vision and for reaching long term disease-free survival.

In Acute myeloid leukemia: The biologic aggressiveness of AML is often anticipated on the underlying chromosome abnormalities and molecular characteristics. Treatment is categorized into induction and consolidation phases. The patients who carry unfavorable cytogenetic or molecular features are likely to undergo stem cell transplantation for consolidation therapy.[40]

In Chronic Lymphocytic Leukemia: Patients having chronic lymphocytic leukemia often do not need therapy at the initial phase as the disease can be indolent course. However, therapy is often indicated for those patients who have constitutional symptoms, hepatosplenomegaly, gross lymphadenopathy, anemia and or thrombocytopenia.[41] The treatment for chronic lymphocytic leukemia has undergone regime changes in the last few years. Although chemotherapy and immunotherapy are considered as first-line treatment, some selective oral agents including ibrutinib, idelalisib and venetoclax are recommended which disrupt several signaling pathways inside the chronic lymphocytic leukemia cell.[42]

In Chronic Myeloid Leukemia: Chronic myeloid leukemia can progress from an indolent chronic phase to a more invasive accelerated or blast phase.[43] The approach with tyrosine kinase inhibitors has extremely upgraded the treatment and prognosis of patients with chronic myeloid leukemia.[44]

PROGNOSIS

Several studies suggest that ophthalmic leukemic infiltrations are more aggressive and have worse outcomes.[45,46] The prognosis also related to some other factors of bone marrow or CSF involvement and the length of initial hematological remission. Among patients with leukemic retinopathy, the mean survival rate was significantly lower who have cotton wool spots, compared with those without those spots. As there is high prevalence of ocular findings in leukemia, it should be a standard practice that all leukemic patients should have a screening through ophthalmic examination.

CONCLUSION

Ophthalmic manifestations of leukemia can result from direct infiltration of leukemic cells or indirect causes along with hematologic abnormalities. It has been observed that mostly all parts of the eye can be involved in leukemia. Sometimes, ophthalmic involvement can be the first sign of disease relapse. Awareness of the clinical spectrum of leukemic infiltration of ocular region is essential for rapid diagnosis, prompt initiation of treatment and better outcome.

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