Review Article

Ophthalmic Manifestations of Acute Leukemia: A Review

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Abstract

Acute leukemias are the most prevalent neoplastic disorder among children. In these patients the leukemic cells or blasts have replaced normal hematopoietic cells in bone marrow and have spread to different extramedullary sites. Increased survival among leukemic patients in recent decades has led to diagnosing some previously less recognized complications among these patients. One of these morbidities is ophthalmic involvement. The presence of ophthalmic involvement among leukemia patients is associated with poor prognosis. Ophthalmic involvement is more common in patients with AML and in adult patients. Leukemia may involve any ocular tissue such as conjunctiva, sclera, cornea, anterior chamber, iris, lens, vitreous, retina, choroid and optic nerve. In this review, the ocular manifestations of leukemia have been discussed.

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Introduction

Acute leukemias are the most common malignant disorder among children [1] and are characterized by uncontrolled proliferation of immature neoplastic cells in bone marrow [1,2]. Typically the leukemic cells or blasts have replaced normal hematopoietic cells in bone marrow and have spread to different extramedullary sites [3]. According to the cell lineage which has been involved, acute leukemia can be divided to acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute mixed lineage leukemia (AMLL) and acute undifferentiated leukemia (AUL) [4]. ALL accounts for about 70 % of all cases of childhood leukemia [5]. The prognosis of childhood ALL is much better than adult ALL [6]. Nowadays the event free survival of children with ALL has improved to 75-85% [7]. These patients often present with anemia, leukocytosis or leukopenia, hepatomegaly, splenomegaly, thrombocytopenia and lymphadenopathy [8]. Both lymphoid and myeloid neoplasms result from abnormalities in genes that control cellular proliferation, survival and differentiation [9].

The hallmark of AML is abnormal proliferation and differentiation of myeloid precursors [10]. The incidence of AML in children is much lower in comparison to ALL[11]. In recent years, in developed countries, intensive treatments including hematopoietic stem cell transplantation combined with effective supportive care has improved the survival rate of these patients to about 70 % in childhood [12]. Increased survival among leukemic patients has led to more recognition of some previously overlooked complications including ophthalmic involvement [13]. Leukemia may affect different ocular tissues including conjunctiva, sclera, cornea, anterior chamber, iris, vitreous, retina, choroid, lens and optic nerve [14]. The presence of ophthalmic involvement is associated with poor prognosis; therefore it is worthy to perform an ophthalmic evaluation at the time of diagnosis of acute leukemia in children and adults [15].

Ocular involvement in acute leukemia can be classified in two categories, direct infiltration by leukemic cells and indirect ocular involvement due to hematological abnormalities such as anemia, thrombocytopenia, blood hyperviscosity or immune suppression [13, 14]. These alterations may lead to hemorrhage, infection or sometimes vascular occlusion [13,14]. Rarely ocular involvement may be the first sign of leukemic relapse [16]. Ophthalmic involvement is more common in AML and more prevalent in adults than in children [15,17]. One of the poor prognostic factors in acute leukemia is central nervous system leukemia, which can be diagnosed using cerebrospinal fluid exam [14, 18]. The most common symptoms of ocular involvement in central nervous system leukemia include diplopia, blurred vision, extra-ocular muscle palsy and optic nerve edema [14]. In this review, ophthalmic manifestations of acute leukemia are discussed.

Pathophysiology

The ocular manifestations of acute leukemia can be divided into two groups [19]. In the primary group, direct infiltration of neoplastic cells in different eye tissues leads to the ocular manifestations [19]. In the secondary group, indirect causes such as ophthalmic injuries due to chemotherapy could be observed [19]. For example immunosuppressive drugs can cause opportunistic infections [20]. Direct leukemic infiltration can involve orbit, anterior segment, uvea and the optic nerve [21]. Consequently papilledema, cranial nerve palsies or proptosis may be observed. Indirect ocular involvement in the majority of cases causes retinal,

pre-retinal and vitreous hemorrhage [15]. Sometimes indirect ophthalmic manifestations occur due to infection in different ocular structures and cause retinal venous occlusion [22].

Ocular toxicity of chemotherapeutic agents

Several chemotherapeutic agents used in treatment of acute leukemia can affect patients' vision [23]. The use of high dose glucocorticoids, especially in induction phase of acute lymphoblastic leukemia may result in increased intraocular pressure, cataracts, glaucoma, dry eye, diplopia and even blindness [24]. Vincristine is a chemotherapeutic agent which is widely used in treatment protocols for ALL. Vincristine can affect motor nerves of the eye (Cranial nerve III, IV, VI and VII) [25, 26]. Also this drug causes optic atrophy [26]. Vinblastine has the same effects and both of these drugs may lead to corneal hypoesthesia [27]. Methotrexate is another drug which has been used extensively in ALL, as oral, intravenous and intrathecal forms [28]. Methotrexate can cause inter-nuclear ophthalmoplegia and optic neuropathy [29, 30]. Cytosine arabinoside is another chemotropic drug which has some toxicity on corneal epithelium [31]. The retinal toxicity of this drug has often been reported with high dose usage and is irreversible in majority of cases [32]. Steroid eye drops have been used in order to prevent corneal toxicity in chemotherapeutic regimes with high dose cytosine arabinoside [33].Cyclosporine is the main drug for prevention of graft versus host disease in recipients of hematopoietic stem cell transplantation [34]. Cyclosporine can cause posterior leukoencephalopathy syndrome [35]. The clinical manifestations of this syndrome include headache, convulsion, change in mental condition and even blindness [36]. Fortunately these presentations can disappear after discontinuation of cyclosporine [36]. Busulfan can cause posterior subcapsular cataracts [37]. Fludarabine might lead to visual disturbances including progressive visual loss with anterior uveitis, blurred vision, vitritis, retinal vasculitis, visual field deficits, optic neuritis, and peripheral retinal necrotic lesions [38]. Imatinib is a monoclonal antibody against B-lymphocyte antigen CD20 and may lead to periorbital edema, blurred vision and conjunctival hemorrhage [39-41].

Ophthalmic manifestations of acute leukemia

Ophthalmic and orbital lesions are the third most common extramedullary involvement in acute leukemias after the meninges and testicles involvement [13]. In some patients, the ocular manifestations of leukemia occur earlier than systemic presentations of hematopoietic malignancy [14]. The ophthalmic signs of leukemia often disappear after the successful chemotherapy and remission of disease but may reappear after the relapse of leukemia [42]. Also the ocular finding of leukemia occur more commonly in the posterior segment in comparison to anterior segment [15]. The most observed findings in the posterior segment include pre-retinal hemorrhage, intra-retinal hemorrhage and retinal hemorrhage with Roth spots [15]. Retinal findings are the most prevalent ophthalmic manifestation in leukemia and retinal hemorrhage is the most common presentation [13,14,43]. There is a strong association between ocular involvement and leukocyte or platelet count in leukemia [19]. Lower platelet count and higher white blood cell count have been correlated with increased incidence of ophthalmic manifestations in leukemic patients [42, 44]. Leukemic manifestations of various eye structures are discussed below in more detail.

Conjunctiva

Conjunctiva is a rare site for leukemic involvement. Conjunctival lesions are more common in lymphocytic leukemia [14]. Comma shaped venous abnormalities may be observed in conjunctiva which are caused by blood hyperviscosity [13, 14]. Conjunctival tumors both in ALL and AML have rarely been reported [45]. Also leukemic patients with thrombocytopenia and subconjunctival hemorrhage have been reported in multiple studies [15, 17, 43, 46, 47].

Cornea

Since cornea is an avascular structure so its involvement is not a common finding in leukemia [14]. Peripheral corneal ulceration, pannus and sterile ring ulcers are some corneal manifestations in leukemia [13, 14, 48]. Keratitis among leukemia patients has been observed due to immunosuppression or graft versus host disease [14]. Graft versus host disease may also cause corneal thinning and consequently corneal perforation in recipients of hematopoietic stem cell transplantation [49].

Iris and anterior segment

The characteristic finding of iris infiltration caused by acute leukemia is a change in iris color and a gray or yellow pseudohypopyon [20]. Infiltration of iris often occurs with involvement of choroid and ciliary body [20]. Sometimes the signs and symptoms of acute glaucoma appear as the intraocular pressure (IOP) is also increased due to infiltration of trabecular meshwork [20]. Another presentation of acute leukemia is spontaneous hyphema [50]. Acute extramedullary relapse of acute leukemia can present as hypopyon uveitis [51]. Occasionally primary relapse of acute leukemia involves anterior chamber segment [14].

Choroidal involvement

Although in histologic evaluation of patients with acute leukemia choroid is more involved than retina the number of clinical retinal involvements is higher [14]. Unilateral or bilateral uveitis, choroidal perivascular infiltration, patchy or diffuse choroiditis, choroidal thickening up to manifold (especially in macular area), retinal pigment epithelium hypertrophy or atrophy, and resultant photoreceptor destruction might also be observed [14, 19, 52]. Also choroidal ischemia due to choriocapillary involvement and serous retinal detachment may occur [42, 43].

Vitreo -retinal involvement

Retina is the most frequent tissue in acute leukemic ocular involvement and accounts for about 75 % of all ocular involvements [53,54]. Sub-retinal, intra-retinal and pre-retinal hemorrhages especially in the macular area might appear with thrombocytopenia as the main cause [55]. They may be flame shape or spot like with a white area at the center caused by the leukemic cells infiltration (Roth spots) [44]. Other retinal features in acute leukemia are vessel dilation, tortuosity and venous aneurism at the peripheral parts of the retina due to blood hyperviscosity [44]. Occasionally retinal vascular sheating may occur due to direct neoplastic cell infiltration [44]. Retinal detachment, unilateral or bilateral retinitis, retinal masses and subretinal hypopyon have also been reported [56]. These retinal masses and infiltrations usually disappear after chemotherapy [14, 42, 52]. Blurred vision in retinal involvement is not usual except in macular involvement or blood penetration to vitreous [17]. Cotton wool spot is seen due to ischemic effects of vascular involvement [14].

Vitreous involvement is not common since the

internal limiting membrane is a barrier like structure which restricts the passage of cells to the vitreous [14].

In addition to these findings bacterial or fungal endophthalmitis is reported due to immune deficiency caused by leukemia itself or its treatments [52]. Other than to infiltrative retinitis there are some opportunist germs such as cytomegalovirus, herpes simplex and herpes zoster viruses which might cause infectious retinitis and occasionally retinal necrosis [51, 57, 58]. Aspergillus and candida might also cause retinitis and vitritis in acute leukemia [58, 59].

It should be noted that chorioretinal involvements of acute leukemia most often appear at the end stages of the disease and should alert us about leukemia progression [42].

Optic nerve and other cranial nerves involvement

Optic nerve involvement in acute leukemia presents with blurred vision and is visible in funduscopy as optic disc edema due to direct leukemic cells infiltration or papilledema due to rising intra cranial pressure [60]. Radiotherapy might arrest the progressive vision loss, but usually the lost vision will not return [61, 62]. CT scan shows optic nerve enlargement due to meningeal thickening [63]. Optic atrophy following long term disc edema can be confirmed with peripapillary OCT (optical coherence tomography) [59, 64].

Cranial nerves involvement might cause diplopia and eye deviation [65]. Some chemotherapeutic medications such as vincristine can cause cranial nerves palsy and resultant lid movement deficit or ocular motility insufficiency [66].

Orbital involvement

Orbital involvement due to acute leukemia is not common. Proptosis is the most frequent feature of orbital involvement. Eye movement limitation, optic disc edema and orbital venous dilation due to pressure effect are some other orbital findings among patients with acute leukemia [13, 67].

Orbital CT scan usually shows diffuse, local or abscess like infiltrations especially in superior and superotemporal sites and pressure effects could be also observed [59, 68]. The other symptoms might be pain, eyelid edema or discoloration towards red or blue, and lid ptosis [69].

Lacrimal gland is an important part of orbital cavity that may be involved in acute leukemia leading to its enlargement and resultant glob deviation towards inferonasal [70]. Lacrimal gland atrophy and dry eye might appear in the long-term involvement [71]. This complication might also be caused by treatment modalities such as chemotherapy or radiotherapy [52].

Orbital masses due to AML are called granulocytic sarcoma [72]. In addition to leukemic orbital masses there are some reports of palpable masses at the superotemporal site of orbit [46]. In some cases of AML the orbital findings appear prior to other leukemia symptoms and their histological results confirm the leukemia sooner than getting a positive bone marrow biopsy or blood smear [46, 73].

In CT scan evaluation, well - defined homogenous isodense masses that occasionally penetrate into paranasal sinuses might be observed [46, 67]. T1 weighted mode MRI might show isointense and T2 weighted MRI might indicate hyperintense masses. In the case of gadolinium injection mild enhancement of the lesion might be observed [46].

Horner syndrome has been observed due to cranial nerve involvement as a rare presentation of acute leukemia [74]. Differential

diagnosis of leukemic orbital lesions are lymphoma, rhabdomyosarcoma, and neuroblastoma [46].

Discussion

In the initial description of ocular involvement in acute leukemia it was described as leukemic retinopathy in the 1860s, but nowadays we know that nearly all eye structures may be affected in leukemia [42]. Ocular involvement among leukemic patients has been reported in various parts of the eye and orbit [14]. The reported prevalence of these ocular involvements shows a wide variation in different studies. This might be caused by different stages of disease among patients entering different studies or the study design. Global and ocular involvements are more common in AML than ALL [13]. Also ocular involvements are more prevalent in adults with leukemia in comparison with children [13]. The importance of regular ophthalmic examination at least every 6 months among patients with acute leukemia is clear especially when considering the close relation of ocular and central nervous system involvement [13].

Management of ocular manifestations of acute leukemia is dependent on these regular eye exams and a close cooperation between the hematologists and ophthalmologists caring for these patients. It should be noted that some ocular manifestations among patients with acute leukemia are the result of therapies used in these patients. There should be a careful evaluation of these therapies harm and benefit before considering their termination. Future advances in diagnostic modalities might lead to early detection of ocular complications of acute leukemia and reduce the chance of irreversible vision loss among patients.

Conclusion

Ocular involvement in acute leukemia can be caused by direct infiltration by leukemic cells or indirect ocular involvement due to hematological abnormalities such as anemia, thrombocytopenia, blood hyperviscosity or immune suppression. It might also bee caused by chemotherapeutic drugs used to treat leukemia. Regular eye exams and a close cooperation between the hematologists and ophthalmologists caring for these patients are essential in reducing the morbidity of these ocular manifestations.

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Footnotes and Financial Disclosures

Conflict of Interest:

The authors have no conflict of interest with the subject matter of the present study.