

Retinal changes in patients with acute lymphocytic leukemia (all): discussion of topic from a case report

Alterações retinianas em pacientes com leucemia linfocítica aguda (lla): discussão de tema a partir de relato de caso

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ABSTRACT

The Acute Lymphocytic Leukemia (ALL) is a disease characterized by a high survival rate, but the absolute number of children who die from it represents a large proportion of cases of infant deaths from cancer. The morbidity resulting from its treatment can leave sequelae in people with high life expectancy, making it extremely necessary to understand the pathogenesis of this disease, enabling the development of new treatments and reduction of sequelae caused by the disease. This early diagnosis is important to avoid ocular complications that may lead to low long-term visual acuity and to evaluate treatment relapses and determine the conducts.

Keywords: Acute lymphocytic leukemia; Leukemical infiltration; Leukemia; Retinal diseases; Papilledema

RESUMO

A Leucemia Linfocítica Aguda (LLA) é uma doença caracterizada por uma alta taxa de sobrevida, porém o número absoluto de crianças que morrem por ela representa uma grande parcela dos casos de óbitos infantis por câncer. A morbidade decorrente de seu tratamento pode deixar sequelas em pessoas com grande expectativa de vida, tornando-se extremamente necessário o entendimento da patogênese desta doença, possibilitando o desenvolvimento de novos tratamentos e diminuição de sequelas provocadas pela doença. O diagnóstico precoce é importante para se evitar complicações oculares que possam levar a baixa de acuidade visual em longo prazo e para avaliação de recaídas de tratamento sendo determinante no direcionamento de condutas.

Descritores: Leucemia linfocítica aguda; Infiltração leucêmica; Leucemia; Doenças retinianas; Papiledema

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The authors declare no conflict of interest

Received for publication 24/6/2020 - Accepted for publication 14/10/2020.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer type; it accounts for 30-35% of all cancer cases in children.⁽¹⁾ It is 4 times more common than acute myeloid leukemia (AML) and reaches its peak between children's 2 and 5 years of age. Ocular changes in ALL are assumingly caused by direct infiltration of the ocular globe and orbit by neoplastic cells. These changes may be secondary to tumor-induced vascular anomalies or related to chemotherapy or glucocorticoids. Early ophthalmic diagnosis is of paramount importance, since ALL is an oncological disease affecting mainly young individuals with high life expectancy. Thus, it can account for high survival rate.

Therefore, the following case report addresses a case of acute ocular involvement in ALL, whose ophthalmic changes were decisive for systemic disease diagnosis and management. This topic was chosen to highlight the importance of ophthalmic oncology examination in determining the appropriate treatment for patients with other diagnoses.

Case report

D.F.R., male, 10 years old, born in Rio de Janeiro City, undergoing treatment in Child Hematology of Federal Hospital of Lagoa (LFH), diagnosed with Acute Lymphocytic Leukemia, was admitted to the Pediatric Intensive Care Unit due to general health impairment and reported progressive visual acuity. The healthcare team requested an ophthalmological opinion, which was provided by a medical resident under the supervision of the medical staff, on December 27, 2018.

The patient presented progressive bilateral visual acuity loss. The following conditions were identified upon bedside ophthalmology examination:

Visual acuity without correction:

Right Eye: 20/200 (according to Snellen's chart). Table-patient distance: 6 meters.

Left Eye: 20/200 (according to Snellen's chart). Table-patient distance: 6 meters.

Indirect biomicroscopy: painless eye (OU), conjunctival pallor (OU), transparent cornea (OU), isochoric pupils (OU), fascia bulbi (OU).

Retinal imaging: papilledema without apparent retinal infiltration (OU), intact macula (OU), hemorrhage in the inferior temporal arcade (OS), 360° retina (OU). The first assessment was not recorded because the patient was in the Intensive Care Unit and could not be transferred - only for Retinography registration.

Cranial computed tomography, performed on the same week of the aforementioned exam, showed optic nerve edema. The patient underwent cranial Nuclear Magnetic Resonance on December 30, 2018, which showed no changes (images are not available because the exam was conducted in another Health Service). Chemoradiation therapy was prescribed due to Central Nervous System involvement.

The Patient underwent a chemotherapy cycle from January 21st, 2019 to February 05th, 2019. However, the patient presented facial paralysis and blurred vision during the therapy. MRI showed leukemic infiltration of cranial nerve pairs and subsequent CNS relapse.

Cerebral / cranial nerve pair MRI performed on February 12th, 2019 showed contrast enhancement of the following regions: distal, tympanic and mastoid segments of the right facial nerve;

geniculate ganglion. There were no signs of leukemic infiltration of grooves, fissures and subarachnoid cisterns. (Images are not available, because the exam was performed in another Health Service).

A new exam was requested by the Ophthalmology Department and scheduled for February 18th, 2019. Retinal imaging evidenced the following: Bilateral optic disc blurring with peripapillary vascular changes; no retinal hemorrhages (OU); Preserved macula (OU), Retinography for registration (Figures 1-12).

The patient was assessed again on May 15th, 2019 at the ophthalmology outpatient clinic. Results showed the following features:

Visual acuity without correction:

Right Eye: 20/70 (according to Snellen chart; table-patient distance: 6 meters).

Left Eye: 20/30 (according to Snellen chart; table-patient



Figure 1: Retinography -2.18.2019



Figure 2: Retinography -2.18.2019



Figure 3: Retinography -2.18.2019



Figure 4: Retinography -2.18.2019



Figure 5: Retinography -2.18.2019



Figure 6: Retinography -2.18.2019



Figure 7: Retinography -2.18.2019

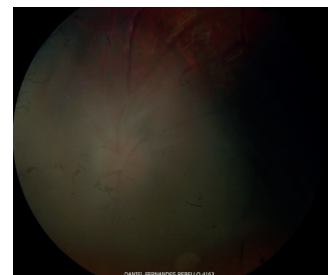


Figure 8: Retinography -2.18.2019

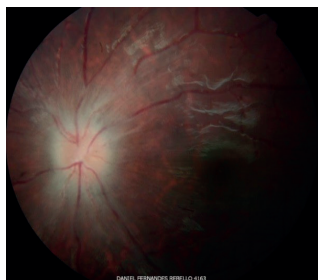


Figure 9: Retinography -2.18.2019



Figure 10: Retinography -2.18.2019



Figure 11: Retinography -2.18.2019



Figure 12: Retinography -2.18.2019

distance: 6 meters).

Biomicroscopy: Normal physiology of eyelashes and eyelids (OU), clear conjunctiva (OU), transparent cornea (OU), inferior limbic keratitis (OU), decreased tear film breakup time (OU), formed anterior chamber (OU), normal iris (OU), isochoric pupils (OU), transparent crystalline lens (OU).

Goldmann tonometry: 12/12 mm Hg at 10:00 a.m.

Retina mapping: staining of the optic disc (OS). Optic disc presenting slight pallor and leukemic deposits (OD). Optical disc margins sharper than those of the last exam (which showed damaged patterns) (OU) Cupping 0.3 x 0.3 (OU). Preserved macular reflex (OU). 360° retina (OU). Artificial tears were prescribed and applied 3 days after new Retinography (OU) for result registration (Figures 13-24).

The disease evolved: the patient reported progressive visual acuity loss in the right eye for 2 days. The patient was admitted to the LFH on July 5th, 2019. A new ophthalmology exam was requested on July 8th, 2019 and performed on the same day in an outpatient clinic.

The patient presented the following:

Visual acuity without visual correction:

Right Eye: Finger count: 3 meters (according to Snellen chart; table-patient distance: 6 meters).

Left Eye: 20/25 (according to Snellen chart; table-patient distance: 6 meters).

Biomicroscopy: Normal physiology of eyelashes and eyelids (OU), clear conjunctiva (OU), transparent cornea (OU), keratitis absent (OU), formed anterior chamber (OU), normal iris (OU),

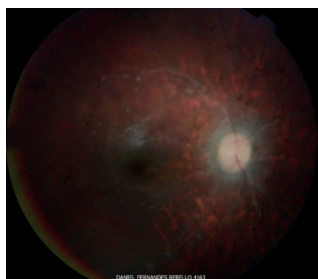


Figure 13: Retinography -5.18.2019

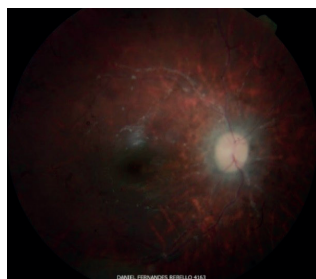


Figure 14: Retinography -5.18.2019

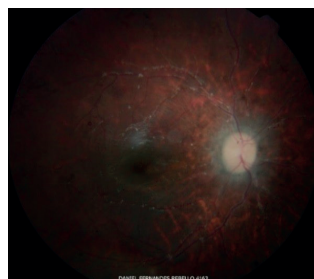


Figure 15: Retinography -5.18.2019



Figure 16: Retinography -5.18.2019

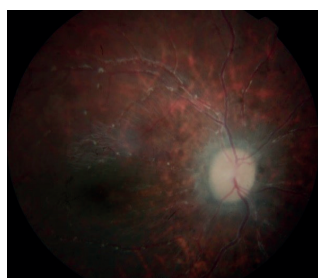


Figure 17: Retinography -5.18.2019

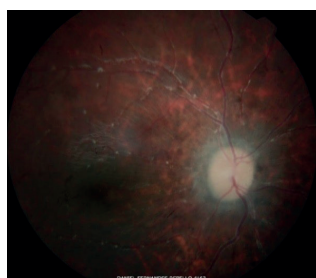


Figure 18: Retinography -5.18.2019

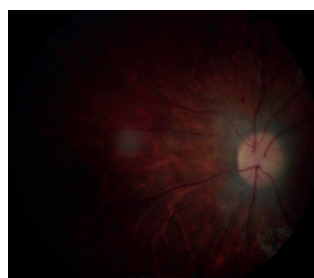


Figure 19: Retinography -5.18.2019



Figure 20: Retinography -5.18.2019



Figure 21: Retinography -5.18.2019

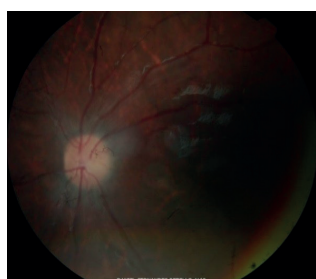


Figure 22: Retinography -5.18.2019



Figure 23: Retinography -5.18.2019



Figure 24: Retinography -5.18.2019

isochoric pupils (OU), transparent crystalline lens (OU).

Goldmann tonometry: 10/13 mm Hg at 10:00 a.m.

Retinal Mapping: papilledema with peripapillary retinal infiltration (right eye's pattern looks more diffuse) (OU). 360° retina (OU). New Retinography was performed for registration (Figures 25-36).

The Pediatric Onco-Hematology Team at LFH and the On-

cology Team at the National Cancer Institute (NCI) discussed the need of radiotherapy. Both teams agreed on chemotherapy only. They decided that radiotherapy, focused on optic nerves, would be recommended only if the decreased visual acuity persisted after the next chemotherapy cycle.

Both teams agreed on avoiding skull and neuroaxis radiotherapy. The patient continued to undergo chemotherapy.



Figure 25: Retinography - 07.08.2019



Figure 26: Retinography - 07.08.2019

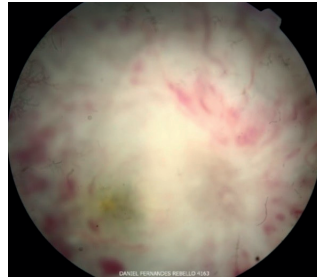


Figure 27: Retinography - 07.08.2019

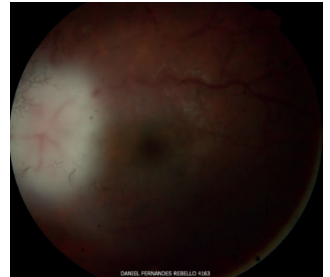


Figure 28: Retinography - 07.08.2019



Figure 29: Retinography - 07.08.2019



Figure 30: Retinography - 07.08.2019



Figure 31: Retinography - 07.08.2019



Figure 32: Retinography - 07.08.2019

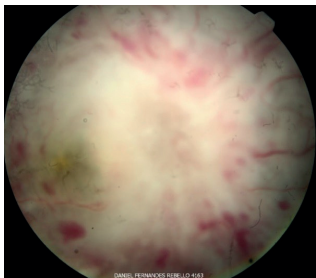


Figure 33: Retinography - 07.08.2019

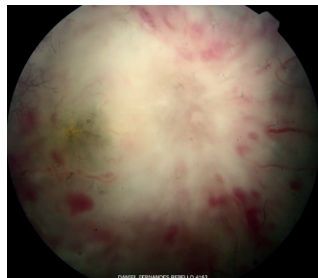


Figure 34: Retinography - 07.08.2019



Figure 35: Retinography - 07.08.2019

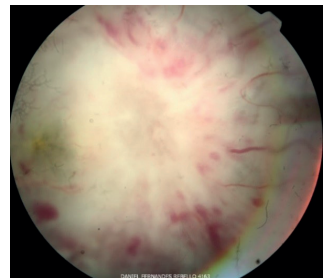


Figure 36: Retinography - 07.08.2019

A new examination was requested by the Ophthalmology Department on September 26th, 2019, as the patient presented severe thrombocytopenia (20.000 platelets) followed by significant drop in hemoglobin and hematocrit levels. The progression of this decrease in the last 8 hours led to mental confusion. Although the examination would be performed in the Pediatric ICU, the patient had to be transferred to another ICU because the hospital's CT scanner was not working.

Visual acuity was not assessed because the patient presented with Glasgow Coma Scale score of 12 upon examination.

Indirect biomicroscopy: painless eye (OU), subconjunctival hemorrhage (OS), transparent cornea (OU), isochoric pupils (OU), fascia bulbi (OU).

Retinal Mapping: optic disc pallor in the right eye (3+/4) with damaged margins, without papilledema (OD). Optic nerve pallor (2+/4+) in the left eye, without papilledema (OS); extensive RPE atrophy (OU); perimacular drusen (OU); 360° retina (OU). The leukemic infiltration evidenced by previous examination was not detected. A new cranial tomography was performed in ano-

ther health unit, which showed no signs of hemorrhage or acute/active bleeding. The patient started on mechanical ventilation and remained in a very serious condition for 3 weeks. The patient died on October 19th, 2019.

DISCUSSION

Leukemias are neoplasms originating from hematopoietic stem cells that proliferate in the red bone marrow before moving into the peripheral blood, spleen, lymph nodes and other tissues. Leukemia classification is based on its originating cell (lymphoid or myeloid), and progression speed (acute or chronic). Acute leukemia results from the clonal proliferation of immature hematopoietic cells. It is divided into acute myeloid leukemia (myeloblasts or promyelocytes) and acute lymphocytic leukemia (lymphoblasts).⁽²⁾

Acute lymphoblastic leukemia is the most common type of childhood leukemia — it accounts for 95% of the cases and for

approximately 70% of leukemia cases in children.⁽²⁾

Ocular involvement is more common in myeloid leukemia than in lymphoid leukemia. Moreover, it is more common in adults than in children.⁽²⁾

Acute leukemia diagnosis is based on laboratory findings and bone marrow biopsy. The Complete Blood Count (CBC) test can detect anemia, thrombocytopenia and white blood cell count — which can be high, low or even within normal limits. Laboratory blood and bone marrow tests are important for acute leukemia diagnosis, since they show leukemic cell infiltration.⁽³⁾

Soft tissues can be affected by blast cell accumulation. However, ocular granulocytic sarcoma may develop prior to bone marrow involvement.⁽⁴⁾

Leukemia treatment is based on combined chemotherapy and radiotherapy (chemoradiotherapy); it can vary according to protocols. It aims at eradicating the largest possible amount of bone marrow lesions. Another treatment approach is bone-marrow transplantation and adjuvant therapy. Immunosuppression and bone marrow suppression are induced in the first treatment phase; they indicate favorable prognosis and good response to treatment. Suppression of hematopoiesis usually leads to the following conditions: anemia, fatigue, skin and mucous membrane pallor, dyspnea, headache, dizziness, heart palpitation, thrombocytopenia manifesting as skin (petechiae and bruises) and membrane mucous hemorrhage.⁽⁵⁻⁷⁾

Ophthalmic leukemia manifestations The eye is the only region presenting evident leukemic involvement of nerves and blood vessels. Eye symptoms are oftentimes the first manifestation of systemic disease or of its relapse after remission induction chemotherapy.⁽⁴⁾

Ophthalmic leukemia manifestations can result from primary/direct leukemic infiltration of ocular tissues or secondary/indirect leukemic ocular involvement.⁽⁸⁾

Direct leukemic infiltration has many patterns, such as: uveal and orbital infiltration, spontaneous hyphema and neuro-ophthalmic symptoms of Central Nervous System involvement. These symptoms include optic nerve infiltration, cranial nerve palsy and papilledema.⁽⁸⁾

Secondary leukemic infiltration results from hematological conditions, such as anemia, thrombocytopenia and hyperviscosity syndrome. Such conditions can manifest as retinal or vitreous hemorrhage, infections and vascular occlusion.⁽⁸⁾ There are also ocular manifestations secondary to antileukemic therapy.

Recent studies have shown that ocular involvement is linked to worse childhood leukemia prognosis. Russo et al.⁽⁹⁾ have demonstrated that specific orbital and ocular lesions in both acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) were associated with high rates of bone marrow relapse and CNS involvement, which lead to decreased survival rate.

Prevalence of ocular involvement in leukemia patients ranges from 9% to 90%, according to several studies.^(4,10-14)

This wide range assumingly results from the transient nature of findings about ophthalmic leukemia manifestations, as they increase and decrease in the course of the disease and of its therapy. It may also result from the diversity of study designs.

Approximately 69% of leukemia patients present changes in the optic fundus at some point of the disease's course.⁽¹⁰⁾ Reddy et al. reported ophthalmic changes in 49.1% of adults and 16.5% of children with leukemia.⁽¹¹⁾

Primary leukemic infiltration (caused by blast cells):

Leukemic infiltration is fairly rare. Direct infiltration by neoplastic cells mainly affects areas with good blood supply, such as

choroid, retina and optic nerve. Avascular tissues, such as cartilage and vitreous tissues, remain unaffected. Orbital infiltrations in hematopoietic cancer patients are rare (approximately 44 cases reported in the literature).⁽¹⁵⁾

Primary orbital involvement is associated with rapidly progressing painful exophthalmos, eyelid edema and conjunctival chemosis (Figure 37).⁽¹⁶⁾ Orbital involvement is most common in children.⁽¹⁶⁾ Direct anterior segment involvement may comprise leukemic iris infiltration, which leads to diffuse thickening followed by iris crypt shrinkage, or iris thickening (formation of nodules at the pupil's margin).^(5,6,17) Extensive iris involvement occurs when leukemic cells penetrate the anterior chamber, forming a pseudohypopyon composed of blast cells.^(15,17) This condition may also lead to increased intraocular pressure — due to direct involvement by neoplastic cell accumulation in the trabecular meshwork —, which manifests itself through the following symptoms: partial or total changes in the iris color, pseudouveitis, corneal marginal ulcers.⁽¹⁸⁾

Both isolated and grouped yellow infiltrates are usually found in the choroid — the most vascularized layer of the eye⁽¹⁾. Manifestations of choroidal involvement are best identified through ultrasound, which can detect diffuse choroidal thickening.

Retinal involvement in leukemia manifests as gray-white nodules of varying size, surrounded by several blastic cells, in the course of chronic leukemias (Figure 38) ⁽¹⁶⁾ On the other hand, vitreous involvement is less common than that of the retina, since the inner vitreous membrane acts as barrier.⁽¹⁾

Cases of CNS leukemia patients have become increasingly common because improved therapy efficacy has led to increased survival rate. Signs and symptoms of CNS involvement include complaints about vision acuity loss, diplopia and extraocular muscle palsy. Such a palsy is associated with cranial involvement and optic disc edema, which can primarily result from direct optic nerve head infiltration or secondarily from increased intracranial pressure.⁽¹⁾

Optic disc edema was detected during the follow-up of the herein reported patient, which implied leukemic CNS involvement. However, a prospective study by Karesh et al.⁽²⁰⁾ showed that none of the patients with optic disc edema had clinical evidence of CNS leukemia. They suggested that it is unreasonable to directly associate disc edema with leukemic infiltration when histopathology has not been assessed.

Optic nerve disease is common in all leukemia types, although it is most common in ALL. Childhood ALL is considered an ophthalmic emergency, since leukemic involvement affects the



Figure 37: Orbital manifestation of acute leukemia. Bowling B. (16).

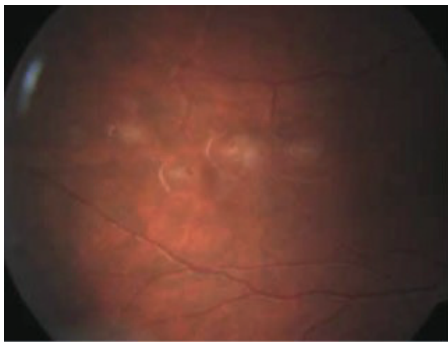


Figure 38: White retinal infiltrates. Bowling B. (16).

patient's vision.⁽²¹⁾

Optic nerve involvement has been reported in 5% to 13% of leukemia patients.⁽²²⁾ Camera et al.⁽²³⁾ reported leukemic optic neuropathy in 1.4% of pediatric ALL cases. Optic nerve infiltration by leukemic cells has rarely been reported in adult ALL patients, who may suffer sudden ALL onset followed by progressive visual acuity loss.

Clinic diagnosis can identify 2 infiltration types, since the pre- and retrolaminar tissues are affected first. Therefore, tumors can either initially stem from the optic papilla, which indicates slow and progressive visual acuity loss, or be detected later in papilledema (Figures 39, 40),⁽¹⁶⁾ which indicates quick vision loss progress.⁽²¹⁾

Damage to the optic nerve is assumingly induced by central nervous system involvement. In this case, patients record survival rate of 50% at 6 months, whereas the mortality rate goes up to 90% within one year.⁽²³⁾

The treatment approach of choice is another relevant concern. Alternative radiotherapy should be considered for treating the intraorbital optic nerve, since this treatment is not covered by chemotherapy due to blood-ocular barriers⁽²⁵⁾.

Sudden vision loss due to unilateral optic nerve involvement is extremely rare; decreased visual acuity may be the only symptom of leukemic optic nerve involvement. Oncologists should be aware of these manifestations in ALL patients, even in remission patients. Other vision-loss causes should always be considered in ALL remission patients, namely: infections, vasculitis, radiotherapy and chemotherapy side effects.

Isolated extramedullary relapse in a previously relapse-free patient suggests that the affected area must have been a sanctuary for leukemic cells during treatment (Figures 41-44).⁽²²⁾ The optic nerve usually remains unaffected during cranial irradiation, when it is chosen as the standard method to treat isolated relapse.⁽²²⁾

Orbital radiotherapy is widely accepted for leukemic optic nerve involvement. A typical 2000 cGy radiation over 1 to 2 weeks for pre- and retrolaminar optic nerve involvement can significantly recover vision and cure clinical abnormalities.⁽²²⁾

Early application of aggressive chemoradiotherapy or hematopoietic stem-cell transplantation should be considered when cranial neuropathy shows signs of systemic relapse. Although salvage therapy is the ideal prophylaxis, it has negative effects on adult ALL patients with central nervous system relapse.

Secondary leukemic changes (caused by indirect eye involvement)

The most common ocular changes in this leukemia type are leukemic retinopathy, acute hyperleukocytosis, peripheral proliferative retinopathy from chronic leukemia and conjunctival vascular abnormalities.

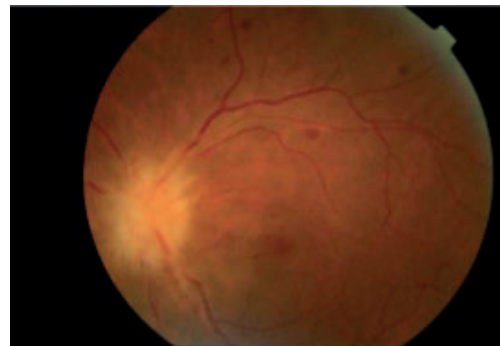


Figure 39: Leukemic optic nerve infiltration associated with retinal hemorrhages. Bowling B. (16)

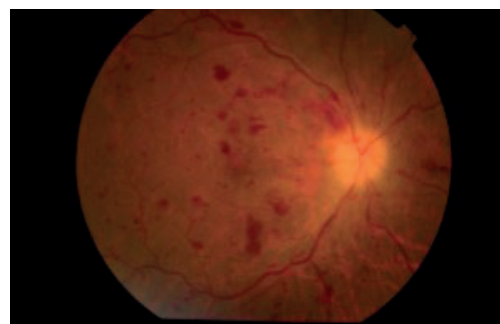


Figure 40: Pale optic disc with blurred margins associated with several peripapillary retinal hemorrhages in all four quadrants. Bowling B. (16)

Leukemic retinopathy, also known as leukemic fundus lesion, is the most common finding. Leukemic retinopathy is defined as a set of retinal changes, such as: dilated and tortuous vessels, white perivascular infiltrates, retinal hemorrhage, platelet and fibrin aggregates or leukemic cell accumulation and cotton wool spots (exudates)⁽¹⁶⁾.

Optic disc hemorrhages are called Roth's spots because they are typically retinal, subhyaloid and pale at the center (Figures 45-52).⁽¹⁶⁾ Roth's spots are intraretinal hemorrhages with whitish centers, which are mostly composed of coagulated fibrin. These spots are common in acute leukemia and other diseases, such as bacteremia, mainly subacute bacterial endocarditis, Systemic Arterial Hypertension (SAH), diabetes and anemia.⁽¹⁶⁾

Retinal hemorrhages are usually asymptomatic, except when they develop in the macula. Other signs and types of retinal hemorrhage can also be found, among them, one finds microaneurysms, peripheral retinal neovascularization, preretinal, subretinal and vitreous hemorrhages. Peripheral retinal neovascularization is an occasional complication of Chronic Myeloid Leukemia (Figure 53).⁽¹⁶⁾ Retinal and choroidal infiltrates may also form; they can be mistaken for posterior uveitis, since they are most commonly found in the posterior equator of the retina. They may present a "leopard spot" pattern in chronic leukemia (Figures 54 and 55).⁽¹⁶⁾

Leukostasis retinopathy is an ophthalmic condition caused by increased blood viscosity (higher than $200 \times 10^9 / L$) from severe hyperleukocytosis.⁽²⁴⁾ Increased circulating leukocytes leads to hyperviscosity, which facilitates the onset of several rare diseases. However, this process is most common in chronic leukemia. Ocular features of hyperviscosity include retinal hemorrhages, venous damage and, occasionally, retinal vein occlusion and conjunctival telangiectasia.

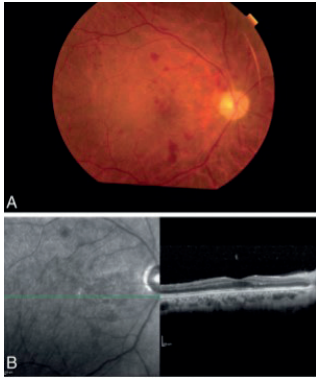


Figure 41: A: Fundus picture after 1 month of curative radiotherapy – pale optic disc with sharp margins and healed retinal hemorrhages. B: Optical coherence tomography showing nasal foveal infiltrates. Nagpal et al. (22).

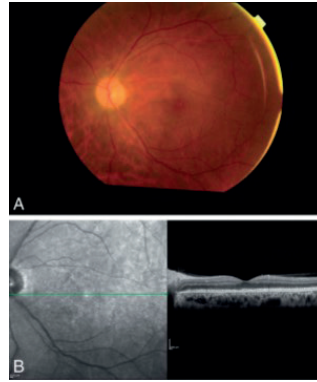


Figure 42: A: Left eye fundus picture after 1 month of curative radiotherapy – normal optic disc with nearly healed retinal hemorrhage. B: Left eye OCT (optical coherence tomography) showing normal study. Nagpal et al. (22).

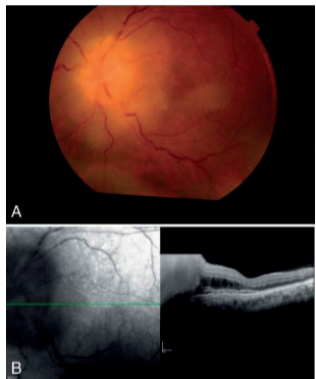


Figure 43: A: Fundus picture showing relapsed ALL evidenced by chronic optic disc edema with leukocyte infiltration. B: Optical coherence tomography showing peripapillary thickening. Nagpal et al. (22).

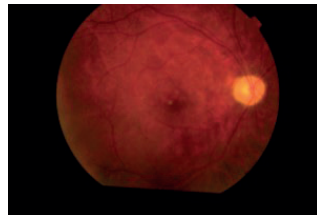


Figure 44: Fundus picture showing pale optic disc with distinct margins. Nagpal et al. (22).

Ocular manifestations secondary to antileukemic therapy

These manifestations can result from the following: opportunistic infections in neutropenic patients, toxicity from chemotherapy and radiotherapy, bone marrow transplant and relapsed malignancy complications. They are mostly apparent in the anterior segment of the eye, where the following evident changes can be detected: keratoconjunctivitis sicca, conjunctivitis (pseudomembranous, bacterial and viral), corneal ulcers, cataracts and glaucoma. Although manifestations of immunosuppression and hematological changes in the posterior segment of the eye are less common, they are severe and present high risk of vision loss.

Combined Immunosuppression and bone marrow failure — typical of leukemia — makes patients very susceptible to opportunistic infections and to the following viruses: cytomegalovirus, herpes simplex virus, varicella-zoster virus and measles morbillivirus. Yet, the most common virus among them is cyto-

megalovirus chorioretinitis.

Cytomegalovirus retinitis is common in immunocompromised patients, mainly in AIDS patients, who can suffer latent infection. If it is not immediately diagnosed, vision loss becomes serious and irreversible. CMV retinitis’ symptoms include visual impairment due to macular involvement and/or floaters due to vitritis. Overall, only one eye is affected at first, but if it is left untreated, it progresses to bilateral involvement in approximately 50% of cases. Mild anterior uveitis followed by little, to no circumlimbal injection, may also result from it. Vitritis is also usually mild; this disease may also induce cataracts, as they are common in the later stage of the disease. (16)

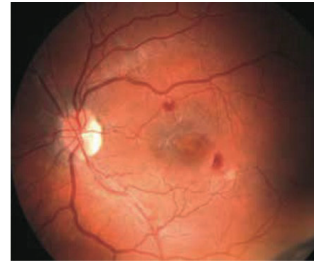


Figure 45: Leukemic optic nerve infiltration: intraretinal hemorrhages, soft exudates and Roth’s spots. Bowling B. (16).

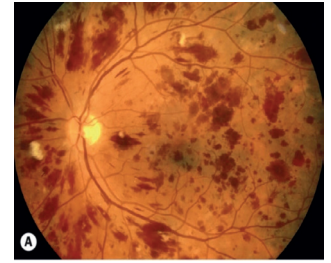


Figure 46: Multiple flame-shaped hemorrhages, cotton wool spots and Roth’s spots. Bowling B. (16).

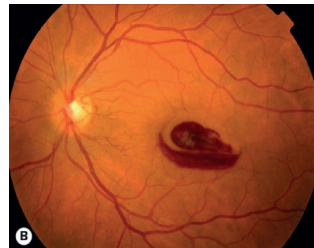


Figure 47: Premacular hemorrhage. Bowling B. (16).

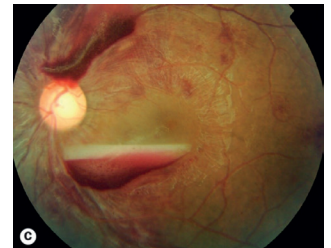


Figure 48: Subhyaloid hemorrhage – clear layer of isolated white blood cells. Bowling B. (16).

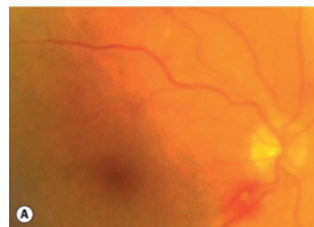


Figure 49: Roth’s spots (typical pattern). Bowling B. (16).

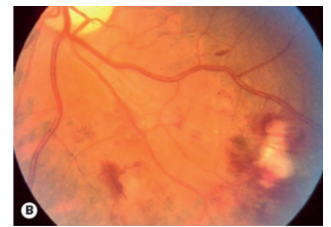


Figure 50: Large Roth’s spots. Bowling B. (16).

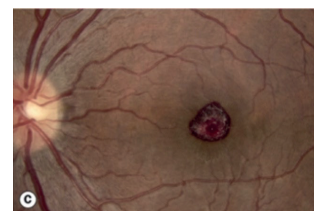


Figure 51: Macular lesion in acute myeloid leukemia. Bowling B. (16).

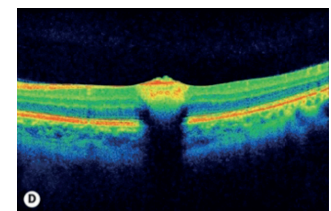


Figure 52: Macular lesion’s OCT in AML (shown in Figure 14). Bowling B. (16).

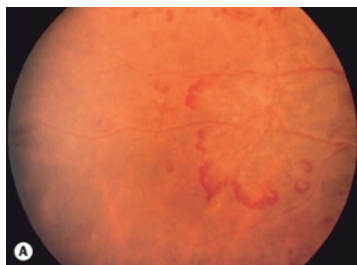


Figure 53: Peripheral retinal neovascularization in chronic myeloid leukemia. Bowling B. ⁽¹⁶⁾.

CMV retinitis typically presents as one or two areas of dense white retinal infiltrates accompanied by flame-shaped (“pizza pie” or “pizza margherita”-shaped) hemorrhages. It starts in the periphery of and extends along arterial arches. Only 10% of them develop in the middle area. The peripheral areas have granular texture with little vasculitis and few round hemorrhages. Two of the CMV retinitis forms are indolent (mostly peripheral and less aggressive) and fulminant (Figures 56-60).⁽¹⁶⁾

Optic neuritis can also arise by direct spread or primary involvement. Retinal necrosis is evident in active inflammation areas; it manifests as irregular pigmentation, holes and atrophies often progressing to retinal detachment. Laser surgery can be performed to treat areas prone to retinal detachment. A vascular sheath (frosted branch angiitis) may develop in approximately 6% of cases. Treatment involves Valganciclovir (ganciclovir prodrug) administration, although it may induce neutropenia. In these cases, filgrastim (granulocyte colony-stimulating factor) administration

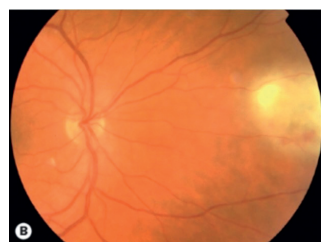


Figure 54: Leukemic choroidal deposits in the retina. Bowling B. ⁽¹⁶⁾.

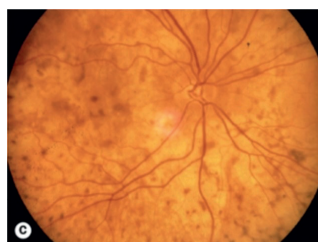


Figure 55: “Leopard spot” pattern due to choroidal infiltration in chronic leukemia. Bowling B. ⁽¹⁶⁾.

is recommended. Vitrectomy with endolaser and silicone oil are assessed individually. Autoimmune disease can also result from leukemia therapy; it is a chronic inflammatory disorder that develops during patients’ immunity recovery. It manifests as extensive anterior uveitis and vitritis, which can be associated with papillitis and cystoid macular edema. This disease requires treatment with corticosteroids.⁽¹⁶⁾

Prolonged exposure to antineoplastic drugs increases the risk of side effects in different organs and tissues. Chemotherapy drugs act in healthy and neoplastic cells at different proportions. Tumor cells have high cell division rate, but other tissues — such as hair follicles and mucous membranes — also present this feature, which makes chemotherapy drugs produce toxic effects.

According to the National Registry of Drug-Induced Ocular Side Effects, the ocular toxicity of antineoplastic drugs can be displayed through changes in both the ocular surface and the tear film, such as: keratoconjunctivitis sicca, conjunctivitis, blepharitis, keratitis, corneal opacity, cicatricial ectropion, periorbital edema,

canalicular stenosis, ptosis, extraocular muscle palsy, diplopia, visual disturbances, cataracts, retinopathy and optic atrophy.^(1,15,25)

Vincristine is one of the drugs used to treat ALL, since it is associated with optic neuropathy. Cytarabine can cause reversible corneal toxicity. Steroid administration is linked to the onset and development of cataracts and glaucoma.

General eye examination should be performed soon after ALL diagnosis. It should include IOP measurement and retinal CT scan. The patient should be closely followed up in the first 6 months after the diagnosis. The need for another ophthalmology examination after this period depends on the symptoms, treatment profile and the patient’s response to it.

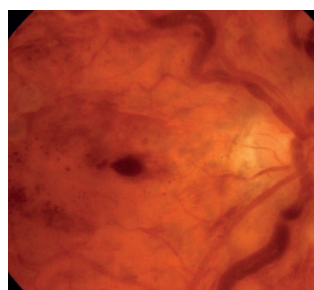


Figure 56: Retinal hemorrhages. Severe retinal vein dilation and segmentation (hyperviscosity). Bowling B. ⁽¹⁶⁾.



Figure 57: Indolent CMV retinitis with typical granular pattern. Bowling B. ⁽¹⁶⁾.

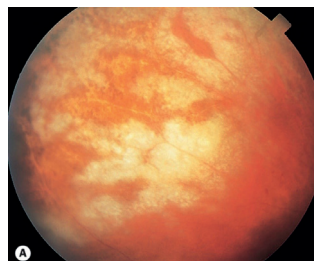


Figure 58: Fulminant CMV retinitis. Bowling B. ⁽¹⁶⁾.

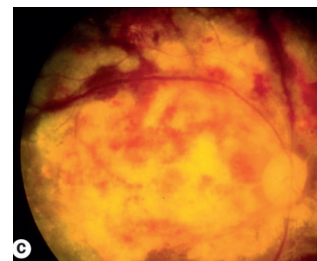


Figure 59: CMV retinitis – Progressive optic nerve head damage. Kanski ⁽¹⁶⁾.

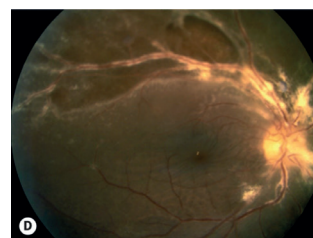


Figure 60: CMV retinitis – Extensive, localized, shallow posterior vitreous detachment. Retinal vascular sheathing deriving from previous frosted branch angiitis. Bowling B. ⁽¹⁶⁾.

CONCLUSIONS

Hospitalized patients with oncological conditions should receive comprehensive care, as changes in certain organs can determine the medical action to be taken. Early eye disease

diagnosis can help preserving patients' eyesight and determining cancer prognosis.

The ophthalmologist should not only identify the pathological and functional changes in the human eye, but also ensure the patient's well-being by clearly and objectively explaining important points of underlying ocular diseases. Kindness in delivering bad news to patients is particularly important in this case, as not only adults, but also children need to take active role in the disease process.

REFERENCES

- Smith OP, Ham IM. Clinical features and treatment of lymphoblastic leukemia. In: Arceci RJ, Hann IM, Smith OP, Hoffbrand A, editors. *Pediatric hematology*. Massachusetts: Blackwell Publishing; 2006. p. 450–81.
- Bitirgen G, Belviranlı S, Caliskan U, Tokgoz H, Ozkagnici A, Zengin N. Ophthalmic manifestations in recently diagnosed childhood leukemia. *Eur J Ophthalmol*. 2016;26(1):88–91.
- Nemcanská S, Stepanov A, Nemcanský J. Ophthalmic manifestations of acute leukaemias. *Cesk Slov Oftalmol*. 2018;74(3):98–101.
- Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. *Surv Ophthalmol*. 1983;27(4):211–32.
- Hejzmanová D, Jebavá R, Hak J, Slavík Z, Vanásek J, Simáková E. [Isolated leukemic infiltration of the iris]. *Cesk Oftalmol*. 1993;49(6):374–9. Czech.
- Hejzmanová D, Langrová H, Jebavá R, Hak J. Unusual ocular findings in children's acute leukemia cases. *Acta Medica (Hradec Kralove)*. 1997;40(2):51–6.
- Rozsival P. *Oční lékařství*. Praha: Karolinum; 2006. p. 323–4.
- Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. *Eye (Lond)*. 2004;18(7):663–72.
- Russo V, Scott IU, Querques G, Stella A, Barone A, Delle Noci N. Orbital and ocular manifestations of acute childhood leukemia: clinical and statistical analysis of 180 patients. *Eur J Ophthalmol*. 2008;18(4):619–23.
- Alemayehu W, Shamebo M, Bedri A, Mengistu Z. Ocular manifestations of leukaemia in Ethiopians. *Ethiop Med J*. 1996;34(4):217–24.
- Reddy SC, Jackson N, Menon BS. Ocular involvement in leukemia—a study of 288 cases. *Ophthalmologica*. 2003;217(6):441–5.
- Buchan J, McKibbin M, Burton T. The prevalence of ocular disease in chronic lymphocytic leukaemia. *Eye (Lond)*. 2003;17(1):27–30.
- Charif Chefchaoui M, Belmekki M, Hajji Z, Tahiri H, Amrani R, El Bakkali M, et al. [Ophthalmic manifestations of acute leukemia]. *J Fr Ophthalmol*. 2002;25(1):62–6. French.
- Lang GE, Spraul CW, Lang GK. [Ocular changes in primary hematologic diseases]. *Klin Monatsbl Augenheilkd*. 1998;212(6):419–27. Germany.
- Yellu MR, Engel JM, Ghose A, Onitilo AA. Overview of recent trends in diagnosis and management of leptomeningeal multiple myeloma. *Hematol Oncol*. 2016;34(1):2–8. Retraction in *Hematol Oncol*. 2017;35(1):142.
- Bowling B. *Kanski oftalmologia clínica: uma abordagem sistêmica*. 8a ed. Rio de Janeiro: Elsevier; 2016.
- Kuchynka P. *Oční lékařství*. Praha: Grada; 2007. p. 733–4.
- Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. *Curr Opin Ophthalmol*. 2016;27(6):545–51.
- Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannan F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP; CONCORD Working Group. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*. 2015;385(9972):977–1010.
- Karesh JW, Goldman EJ, Reck K, Kelman SE, Lee EJ, Schiffer CA. A prospective ophthalmic evaluation of patients with acute myeloid leukemia: correlation of ocular and hematologic findings. *J Clin Oncol*. 1989;7(10):1528–32.
- Hong SS, Park HR, Kim KS, Choi SH. [Late effects, social adjustment, and quality of life in adolescent survivors of childhood leukemia]. *J Korean Acad Nurs*. 2014;44(1):55–63. Korean.
- Nagpal MP, Mehrotra NS, Mehta RC, Shukla CK. Leukemic optic nerve infiltration in a patient with acute lymphoblastic leukemia. *Retin Cases Brief Rep*. 2016;10(2):127–30.
- Camera A, Piccirillo G, Cennamo G, Tranfa F, Rosa N, Frigeri F, et al. Optic nerve involvement in acute lymphoblastic leukemia. *Leuk Lymphoma*. 1993;11(1–2):153–5.
- Lyu S, Zhang M, Gao Y. Acute bilateral retina hemorrhages beneath internal limiting membrane: an unusual ophthalmological case report of acute leukemia during complete clinical remission. *Medicine (Baltimore)*. 2018;97(7):e0000.
- Fraunfelder FT, Meyer SM. Ocular toxicity of antineoplastic agents. *Ophthalmology*. 1983;90(1):1–3.

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