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CASE REPORT

Case report: Orbital recurrence of Acute Lymphoblastic Leukemia (ALL) in children

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Abstract

Introduction: The recurrence of childhood ALL involving the eyeball is a rare event, occurring in 2.2% of children. The presence of specific orbital and ocular lesions is associated with a higher frequency of bone marrow relapses and CNS involvement, leading to a lower survival rate. **Objectives:** Conduct a longitudinal observational analysis of cases of orbital recurrences of ALL in children undergoing treatment at a reference oncology hospital in Western Paraná. **Case Report 1:** 1-year-old female patient, undergoing treatment for ALL, presented with a whitish lesion in her left eye. In consultation with an ophthalmologist, an alteration of the red reflex with vitritis was observed in the left eye, and in the right eye an elevated lesion suggestive of an intraocular mass was seen. After months of investigation, it was concluded that there was orbital recurrence of ALL, and treatment was initiated according to BFM-90 for recurrences. **Case Report 2:** 2-year-old female patient, undergoing treatment for ALL, presented skin lesions, right periocular edema and divergent strabismus. MRI of the orbit showed diffuse thickening of the optic nerves in their intraconal and canicular segments and part of the cisternal path, suggestive of infiltration of the optic nerves by the underlying disease. After confirming the diagnosis of ALL orbital recurrence, treatment was carried out according to the BFM-90 protocol. **Conclusion:** Through this research, the importance of a thorough evaluation of ophthalmological signs and symptoms in patients diagnosed with ALL was evidenced, for an early diagnosis and treatment.

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INTRODUCTION

Acute Lymphocytic Leukemia (ALL) is a disease characterized by a high survival rate in children, but the absolute number of children who die from it represents a large portion of cases of childhood deaths from cancer.[1]

Recent studies have demonstrated that ocular involvement is related to the worse prognosis in childhood leukemia. Relapse of childhood ALL involving the eyeball is a rare event, occurring in 2.2% of relapsing children.[2] In both acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), specific orbital and ocular lesions have been associated with a higher frequency of bone marrow relapses and CNS involvement, leading to a lower survival rate.[3] Orbital infiltration occurs particularly in children, and it is associated with rapidly developing painful protrusion of the eyeball, eyelid edema, and conjunctival chemosis.[1]

Early diagnosis is important to avoid ocular complications that could lead to long-term reduced visual acuity and to evaluate treatment relapses, being crucial in directing management.[1]

CASE REPORT 1

A 1-year-old female patient, previously healthy, in September 2019 started with fever that had not been measured for 1 week, groaning, pallor, laboratory tests were carried out suggestive of Acute Lymphoid Leukemia (ALL) and then referred to the oncology service of reference in Western Paraná. Confirmed diagnosis of ALL, pre-B High Risk. Treatment began in September 2019 and went into maintenance in August 2020.

During the beginning of maintenance, the mother reported the appearance of a whitish lesion on her left eye. In consultation with an ophthalmologist, a change in the red reflex with vitritis in the left eye and right eye was found, and an elevated lesion was seen, suggestive of an intraocular mass. Computed Tomography (CT) of the skull and orbits was ordered, showing intraocular tissue in the posterior region close to the insertion of the optic nerve bilaterally, with a suspicious appearance of a neoplastic lesion. The diagnostic hypothesis of bilateral retinoblastoma was suggested.

After 2 months of investigation, an ocular ultrasound was performed revealing a tumor lesion on the optic nerve in the right eye, suggestive of leukemic infiltration. In a joint investigation with other pediatric oncology centers in Curitiba-PR and São Paulo-SP, the diagnosis of Ocular Isolated Extramedullary Relapse of ALL was reached.

Chemotherapy (CT) was started, with the Berlin-Frankfurt-Munich (BFM-90) protocol for relapse, as shown in Table 1, after Bone Marrow (BM) aspirate, immunophenotyping and negative Minimal Residual Disease (MRD). A new CT scan of the orbits was performed, suggesting a therapeutic response established after the start of treatment.

Patient began follow-up with an oncological ophthalmologist in São Paulo. During the two-year follow-up, there was progressive regression of the tumor mass and improvement in the serous retinal detachment.

After joint discussion between the medical team and those responsible for the minor, she was registered in the bone marrow transplant service at a reference oncological institution with greater complexity in Paraná. Currently, she remains on

Table 1. BFM 90 Protocol.

Drug	Dose and administration pathway	Treatment day
HR1 Block		
- Dexamethasone	20 mg/m² PO	1-5
- mercaptopurine	100 mg/m² PO	1-5
- vincristine	1.5 mg/m² (up to 2 mg) IV	1,5
- methotrexate (+Folinic acid [&])	5,000 mg/m² IV (in 24 h)	1
- cytarabine	2,000 mg/m² IV (12/12 h)	5
- L-asparaginase	25,000 U/m² IM	6
- methotrexate	6-12 mg IT *	1
- cytarabine	16-30 mg IT #	1
- prednisolone	4-10 mg IT ##	1
HR2 Block		
- dexamethasone	20 mg/m² VO	1-5
- tioguanine	100 mg/m² VO	1-5
- vindesine	3 mg/m² (up to 5 mg) IV	1
- methotrexate (+ ac. Folinic [&])	5.000 mg/m² IV (in 24 h)	1
- ifosfamide	400 mg/m² IV (in 1 h)	1-5
- daunorubicin	50 mg/m² IV (in 24 h)	5
- L-asparaginase	25.000 U/m² IM	6
- methotrexate	6-12 mg IT *	1
- cytarabine	16-30 mg IT #	1
- prednisolone	4-10 mg IT ##	1
HR3 Block		
- dexamethasone	20 mg/m² VO	1-5
- cytarabine	2.000 mg/m² IV (12/12 h)	1, 2
- etoposide	150 mg/m² IV (em 1 h)	3-5
- L-asparaginase	25.000 U/m² IM	6
- methotrexate	6-12 mg IT *	5
- cytarabine	16-30 mg IT #	5
- prednisolona	4-10 mg IT ##	5
Maintenance###		
- mercaptopurine	50 mg/m²/day PO	
- methotrexate	mg/m²/week PO	

PO: per os, IV: intravenous, IT: intrathecal, IM: intramuscular, CNS: central nervous system.
*according to age: < 1 year, 6 mg / ≥ 1 year and < 2 years, 8 mg / ≥ 2 years and < 3 years, 10 mg / ≥ 3 years, 12 mg.
** Only for basic and intermediate risk.
*** It is used after administering cyclophosphamide for hemorrhagic cystitis prophylaxis.
[&] Folic acid is administered to help eliminate the methotrexate.
[&&] Only for basic risk.
[&&&] For high risk Only. Each block is repeated twice in the following order: HR1, HR2 and HR3.
[#] According to age: < 1 year, 16 mg / ≥ 1 year and <2 years, 20 mg / ≥ 2 years and <3 years, 26 mg / ≥ 3 years, 30 mg.
[##] According to age: < 1 year, 4 mg / ≥ 1 year and < 2 years, 6 mg / ≥ 2 years and < 3 years, 8 mg / ≥ 3 years, 10 mg.
[###] Doses are adjusted according to the leukocyte blood Count. For all the patients, maintenance lasts until completing 24 months of treatment.
Source: Pediatrics Journal.[4]

the waiting list for a BM transplant and remains monitored and treated by the pediatric oncology service.

CASE REPORT 2

A 2-year-old female patient, with no previous comorbidities, started with pain in the left lower limb, limping and intermittent fever. X-ray and CT were performed in the city of origin, both without changes. Blood count with changes suggestive of ALL.

After evaluation at the oncology institution, she was diagnosed with ALL. She started treatment in January 2021 and went into maintenance in November 2021, according to the BFM-90 protocol.

During maintenance, the patient developed skin lesions, periocular edema on the right and divergent strabismus. She was referred for ophthalmological evaluation, which revealed low visual acuity and strabismus in the left eye, without ophthalmological causes or the presence of leukocoria. Magnetic Resonance Imaging (MRI) of the orbit revealed diffuse thickening of the optic nerves in their intraconal and canicular segments and part of the cisternal path, suggestive of infiltration of the optic nerves by the underlying disease.

Soon after, a lumbar puncture was performed with a positive result for recurrence of type B ALL. After diagnosis, the patient began follow-up with an ophthalmologist at a referenced institution, and the BFM 90 protocol for recurrence was initiated (table 1).

After 6 months of treatment, the right eye regained full vision. However, the left eye had permanent damage due to atrophy of the optic nerve. It is concluded that the treatment resulted in a significant improvement in the right eye vision.

Currently, she is clinically stable, with unchanged orbital lesion, without progression. She continues to be maintained and monitored by the pediatric oncology hospital.

DISCUSSION

Leukemia causes several changes in the individual's body, with ophthalmological manifestations being rare. These changes occur due to direct infiltration of the orbit and eyeball by neoplastic cells or even as a result of compounds used in the treatment, or secondary to vascular abnormalities induced by the tumor itself.[1]

Some studies show that the worst prognosis for childhood leukemia is related to ocular involvement. Ocular and orbital lesions were associated with a greater number of recurrences of medullary leukemias with CNS involvement, resulting in a higher mortality rate.[3]

As for ocular symptoms, they can happen in three ways: they can be presenting signs of leukemia, they can appear after the diagnosis is established or they can be the first manifestation of a relapse after remission.[5]

In view of this, it is of great importance to observe the patient's signs and symptoms related to CNS involvement, among the complaints we can mention diplopia, loss of vision focus, extraocular muscle paralysis and optic disc edema, which may be the result of increased intracranial pressure or even due to the infiltration of leukemic cells in the optic nerve.[6]

According to current literature, there is still little association between optic nerve involvement and the presence of blasts in cerebrospinal fluid cytology, which reinforces the importance of ocular signs.[7]

Relapses of Acute Lymphoid Leukemia (ALL) can occur in an isolated extramedullary manner or first affect the bone marrow and, only then, to extramedullary locations. In some cases, ocular symptoms may be the first indication of disease recurrence.[8]

In both reported cases, ocular symptoms preceded other changes caused by ALL recurrence. However, treatment according to the BFM-90 protocol resulted in a good therapeutic response, despite not having been curative at the time of the study.

CONCLUSION

Despite few reported cases of ocular recurrence of ALL, this study demonstrated the importance of a thorough evaluation of ophthalmological signs and symptoms so that early detection of the disease in the extramedullary form can be carried out, whether in patients diagnosed with ALL, regardless of the treatment phase or even after remission.

Finally, in addition to early diagnosis, it is essential to start chemotherapy treatment as soon as possible according to the experience of each service. Since in both clinical cases there was tumor regression after starting treatment.

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