

## Orbital relapse in children treated for Pre-B ALL, a retrospective case series

Komal Seher, Saadiya Javed Khan

### Abstract

About 85-90% of children with B-cell leukaemia are cured. If relapse occurs it is usually in the bone marrow (BM), followed by extramedullary sites. Ocular lesions occur secondary to the accumulation of circulating blasts in the uvea, optic disc, intra-ocular tissue as well as fluid. Here we report four patients with ocular complaints that led to the diagnosis of relapse. Among 475 children with leukaemia treated from January 2013 to December 2018, 50 (10.5%) patients relapsed. Four (8%) out of these 50 presented with orbital symptoms. Central Nervous System (CNS) evaluation by cerebrospinal fluid (CSF) was negative at relapse. Relapse was treated with chemotherapy R3 protocol. Three (75%) patients are alive, while the fourth patient had a second BM relapse and died. Ophthalmic signs and symptoms in patients with treated leukaemia warrant a thorough evaluation. These signs can be an indication of relapse. BM and CSF studies should be done for diagnosing relapse.

**Keywords:** Ocular relapse, Paediatric leukaemia, Bone marrow, Central nervous system (CNS), Ophthalmic signs.

**DOI:** <https://doi.org/10.47391/JPMA.1053>

### Introduction

About 85-90% of children with B-cell leukaemia are cured with the current chemotherapeutic regimens.<sup>1,2</sup> Cure rates are lower in lower-middle income countries (LMICs) where majority of children with Leukaemia reside.<sup>3</sup> Relapses usually occur in the bone marrow (BM) followed by extramedullary sites such as the central nervous system (CNS) and testicles.<sup>4</sup> Orbital and ocular lesions are rare.

Apart from sites, relapse can also be classified according to the duration from remission or end-of-treatment. Very early relapse is defined as occurring less than 18-months, early relapses are those between 18-36 months, and late relapse are more than 36-months from diagnosis. While predicting survival, physicians take into account the site of relapse as well as the duration of first

complete remission.<sup>5</sup>

Approximately 30-50% of children with relapse are cured in the developed world, whereas there is a paucity of data on types of relapse, treatment offered and disease outcomes in LMICs like ours.<sup>6</sup> Here we report our findings of orbital relapse in four children out of 50 who relapsed from a total of 475 children who completed treatment for acute leukaemia at Shaukat Khanum Memorial Cancer Hospital in Pakistan. Approval from institutional review board and consent from parents of all the children was taken for data collection and publication.

### Case Presentation

**Patient 1:** A seven-year old girl with a history of acute pre-BALL who was in remission for about two years presented in April 2017 with redness, watering and discharge from the left eye. She was started on antibiotics and an examination was done under anaesthesia (EUA). The examination showed left eye moderate conjunctival congestion, mildly hazy cornea, regular pupil with mid-dilated crystalline lens and a normal fundus. The right eye anterior segment and fundus was normal. Initially she was given topical ophthalmic steroid and Levobunolo drops. Three-months later she started having symptoms in the right eye. A second EUA showed severe conjunctival congestion, pseudohypopyon, 360° degrees posterior synechiae with a normal right fundus in the right eye. Facilities to perform anterior chamber paracentesis were not available. Bone marrow biopsy was positive and CSF studies were negative. MRI of the brain was normal.

**Patient 2:** A seven-year old boy presented in March 2017 with bilateral conjunctivitis, three-months after finishing maintenance chemotherapy for Pre-BALL that responded to topical antibiotics. Four-months later he again presented with left eye symptoms. EUA showed moderate conjunctivitis, pseudohypopyon, and posterior chamber synechiae with a poor fundus view. The right eye anterior and posterior chambers were normal. No brain imaging was done for this child. BM showed blasts but CSF was clear.

**Patient 3:** A 7.5-year-old boy presented with bilateral conjunctivitis and photophobia in July 2017 during his 10th maintenance cycle of chemotherapy for Pre-BALL.

.....  
Department of Pediatric Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan.

**Correspondence:** Komal Seher. Email: [komalseher@skm.org.pk](mailto:komalseher@skm.org.pk)

**Table-1:** Patient characteristics with first relapse of ocular ALL.

Patient	Age (years)	Sex	Ocular symptoms at presentation	Time from end-of-therapy to ocular symptoms (months)	Time from ocular symptoms to bone marrow relapse (months)
1	7	Female	Red, painful left eye. Three months later developed right eye redness & pain as well	4	6
2	7	Male	Redness in both eyes. Four months later presented with painful left eye	3	5
3	7.5	Male	Bilateral painful and red eyes	Relapsed during therapy	3
4	6	Male	Bilateral painful and red eyes	8	12

He was empirically treated with intravenous antibiotics, and was also given topical steroid eye drops and Cyclopentolate by the ophthalmologist. EUA showed vitreous lesions, retina appeared flat and optic nerve appeared normal. While he was on antibiotics, blasts were reported on his peripheral blood (PB). Bone marrow had blasts but the CSF was clear.

**Patient 4:** A six-year old boy with Pre-B-ALL presented in February 2018 with bilateral tearing and red eyes eight months after finishing chemotherapy. EUA showed conjunctivitis and left anterior chamber pseudohypopyon. The family was advised to get CSF and BM studies. But instead they kept using the topical steroids advised by the ophthalmologist that did help relieve symptoms temporarily. He again presented, six-months after this EUA, with pain and persistent redness of eyes. This time CSF and BM studies were done and showed isolated BM relapse.

**Management and outcome:** Patient 1 was treated with systemic chemotherapy as per the R3 chemotherapy protocol. She is well and alive as per her last follow-up visit.

Patient 2 was started on R3 chemotherapy protocol. He is currently doing well on monthly follow-ups.

In patient 3 palliation was initially offered, given the rapid presentation of ocular symptoms and blasts on PB while he was on oral chemotherapy. The family insisted on curative options and hence he was also started on R3 chemotherapy protocol. He was in remission completing R3 maintenance cycle when he developed severe pneumonia and blasts were seen on PB. He succumbed to infection while he relapsed for the second time.

Patient 4 was started on R3 protocol and is currently doing well in remission.

## Discussion

Relapse in ALL is heart-breaking and a common cause of treatment failure. In our centre the relapse rate was 10.5%, that is, less than that seen in the developed world.<sup>7</sup> This is because we are treating young children with standard risk leukaemia only. Ocular symptoms in

children treated for leukaemia or during therapy of leukaemia should be taken seriously. In a series of 898 relapses, 20 intraocular patients were analysed by Somerville et al accounting for a prevalence of 2.2%.<sup>8</sup> In our cases the rate was higher at 8%.

Ocular relapse can happen during or at the end of leukaemia therapy. The initial period after discontinuation of chemotherapy is crucial for anterior chamber relapse.<sup>9</sup> Relapse from the time of diagnosis has a prognostic effect. Shorter duration leads to worse consequences. Patient 3 was the only patient who relapsed during chemotherapy and hence was at high risk with a grim prognosis. Patient 1, 2 and 4 all presented with symptoms post treatment. These children took time manifesting their relapse after the emergence of their ocular signs. Unfortunately, we do not have access to diagnostic procedures such as anterior chamber paracentesis, iris biopsies, etc.

Ohkoshi et al showed that majority of the patients with ocular relapse also had CNS relapse. They showed a five-year survival rate of 21.4% in patients with ocular leukaemia as compared to 45.7% in those without ocular symptoms.<sup>10</sup> In our series, none of the patients had CNS leukaemia. Instead they all had combined ocular and BM relapse. Our follow up period is short but for now three out of four patients are alive. We will need to follow these patients closely to determine our five-year survival rate.

Lo et al reported a retrospective multicentre study of 21 patients who were treated with chemotherapy and some of them also had radiation therapy to the affected eye. Long-term outcomes are favourable for patients who had both therapies with visual compromise in the eye that was subjected to radiation.<sup>11</sup> In our series except for patient 3, all the others had late relapse and, hence, we decided to adopt intensive systemic chemotherapy and avoid ocular radiation. These children will need to be followed very closely knowing that their eyes might remain a sanctuary for leukaemic cells during treatment.

## Conclusion

A limitation of our case series is the unavailability of

benign ocular symptoms that occur in ALL patients post treatment. But despite this we emphasise that all ocular complaints in children with a history of leukaemia should be cautiously evaluated to pick up early relapse. With our limited resources, working in a LMIC, we were not able to obtain anterior chamber fluid or ocular biopsies and hence, waited for relapse to manifest in the bone marrow. In our series the outcomes were better for those in whom ocular relapse occurred after completion of initial therapy.

**Disclaimer:** None to declare

**Conflict of Interest:** None to declare

**Funding Disclosure:** None to declare

## References

1. Pui CH, Evans WE. Treatment of acute lymphoblastic leukaemia. *N Engl J Med*. 2006;354:166–78.
2. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukaemia between 1990 and 2005: A report from the children's oncology group. *J Clin Oncol*. 2012;30:1663–9.
3. Abboud MR, Ghanem K, Muwakkit S. Acute lymphoblastic leukaemia in low and middle-income countries: disease characteristics and treatment results. *Curr Opin Oncol*. 2014;26:650–5.
4. Malempati S, Gaynon PS, Sather H, Mei K La, Linda C Stork, Children's Oncology Group. Outcome after relapse among children with standard-risk acute lymphoblastic leukaemia: Children's Oncology Group study CCG-1952. *J Clin Oncol*. 2007;25:5800–7.
5. Locatelli F, Schrappe M, Bernardo ME, Rutella S. How I treat relapsed childhood acute lymphoblastic leukaemia. *Blood*. 2012;120:2807–16.
6. Mushtaq N, Fadool Z, Naqvi A. Childhood acute lymphoblastic leukaemia: experience from a single tertiary care facility of Pakistan. *J Pak Med Assoc*. 2013;63:1399–404.
7. Kamps WA, van der Pal-de Bruin KM, Veerman AJP, Fiocco M, Bierings M, Pieters R. Long-term results of Dutch childhood oncology group studies for children with acute lymphoblastic leukaemia from 1984 to 2004. *Leukaemia*. 2010;24:309–19.
8. Somerville TC, Hann IM, Harrison G, Eden TO, Gibson BE, Hill FG, et al. Intraocular relapse of childhood acute lymphoblastic leukaemia. *Br J Haematol* 2003; 121: 280-8.
9. MacLean H, Clarke MP, Strong NP, Kernahan J, Ashraf S. Primary ocular relapse in acute lymphoblastic leukaemia. *Eye (Lond)* 1996; 10 : 719-22.
10. Ohkoshi K, Tsiaras WG. Prognostic importance of ophthalmic manifestations in childhood leukaemia. *Br J Ophthalmol* 1992; 76: 651-5.
11. Lo CM, D'Angelo P, Lumia F, Provenzano G, Zingone A, Bachelot C, et al. Leukemic ophthalmopathy: a report of 21 paediatric cases. *Med Paediatr Oncol* 1994; 23: 8-13.