Ophthalmic Manifestations In Patients of Acute Leukaemia Presenting to A Tertiary Care Centre In Western Rajasthan

Shilpi Kochar, Yamini Singhal, Jaishree Murli Manohar, Kalpana Jain
Department of Ophthalmology, Sardar Patel Medical College, Bikaner, Rajasthan, India

Purpose:- To determine the prevalence and pattern of ophthalmic manifestations in patients of Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL) presenting to a tertiary care centre in Western Rajasthan.

Materials and Methods: This cross-sectional non-interventional study was conducted from April 2015 to March 2016 to study the spectrum of ophthalmic manifestations in 110 acute leukaemia patients. Patient’s demographic data, medical and treatment history, anterior and posterior segment examination with haematological and radiological investigations were recorded.

Results:- The study subjects (n = 110: 57 males and 53 females) comprised 64 ALL and 46 AML patients whose age ranged from 22 months to 58 years. There were 44 adults and 66 children. Leukemic ophthalmopathy was present in 61 (55.45%) subjects. Ocular changes were present in 30/44 (68.18%) adults and 31/66 (46.97%) children (P<0.04). Thirty four males (34/57, 59.65%) and 27/53 (50.94%) females had ocular manifestations (P<0.46). The leading posterior segment ophthalmic manifestation was superficial haemorrhage and the anterior segment manifestation was sub-conjunctival hemorrhage. Primary or direct leukemic infiltration was seen in 11 (10%) subjects while secondary or indirect involvement was seen in 60 (54.54%) subjects. Leukemic ophthalmopathy was more prevalent in Acute Myeloid Leukemia in comparison to Acute Lymphoid Leukemia, frequently affected the ocular posterior segment and often resulted from secondary hematologic complications (P <0.001).

Conclusion:- Leukemic ophthalmic lesions were found in 61/110 (55.45%) patients. Ocular involvement is more often seen in Acute Myeloid Leukemia. Early diagnosis and regular ophthalmic examinations are recommended to optimize diagnosis, prognostic and treatment outcomes of Acute Leukaemia patients.

Keywords: Leukemia, retinal haemorrhage

Introduction
Leukaemias are malignant neoplasms of the haematopoietic stem cells, characterized by diffuse replacement of the bone marrow by neoplastic cells and widespread infiltration of organs, tissues and peripheral blood by immature leucocytes. The resultant displacement of normal hematopoietic stem cells from the bone marrow leads to secondary hematologic complications such as erythrocytopenia, thrombocytopenia and leukostasis. Although there is peripheral leucocytosis, the circulating leucocytes are immature and dysfunctional. These secondary hematologic alterations are responsible for tissue ischemia, bleeding diathesis, immune-suppression, and hyperviscosity state which are the cardinal pathologic features of leukemia.

With evolving diagnostic and therapeutic advances, the survival of patients with acute leukaemia has considerably improved. This has led to an increase in the variability of ocular presentations in the form of side effects of the treatment and the ways leukaemic relapses are being first identified as an ocular presentation. Leukaemia may involve any ocular tissues either by direct infiltration, haemorrhage, ischaemia, or toxicity due to various chemotherapeutic agents. Ocular involvement may also be seen in graft-versus host reaction in patients undergoing allogeneic bone marrow transplantation, or simply as increased susceptibility to infections as a result of immunosuppression that these patients undergo.

Ophthalmic involvement can be classified into two major categories:
1. Primary or Direct leukaemic infiltration
2. Secondary or Indirect involvement.

The Direct leukaemic infiltration can show three patterns:
anterior segment uveal infiltration, orbital infiltration, (Figure 1) and neuro-ophthalmic signs of central nervous system leukaemia that include optic nerve infiltration, cranial nerve palsies, and papilloedema. The Secondary changes are the result of haematological abnormalities of leukaemia such as anaemia, thrombocytopenia, hyperviscosity, and immunosuppression. These can manifest as retinal or vitreous haemorrhage, infections, and as vascular occlusions. In some cases the ocular involvement may be asymptomatic. In one prospective study, there was a high prevalence of asymptomatic ocular lesions in childhood acute leukaemia. In the era before effective anti leukaemic therapy, retinopathy was believed to be of no prognostic significance in acute leukaemia. However, recent reports have demonstrated that the presence of ocular involvement is associated with poor prognosis in acute childhood leukaemias. Therefore, it is important to consider an ophthalmic evaluation at the time of diagnosis of acute leukaemia in adults and children. Recognition of the varied ocular presentations is also important in assessing the course and prognosis of leukaemia. We have presented a systematic approach by conducting detailed ophthalmological examination of every part of the eye and outlining how leukaemia has been shown to affect it.

Materials and Methods
This cross-sectional non-interventional study was conducted from April 2015 to March 2016 in Department of Ophthalmology, S.P. Medical College, Bikaner in

| Primary/Direct changes                      | No. | Secondary/Indirect changes | No. |
|--------------------------------------------|-----|-----------------------------|-----|
| Proptosis due to orbital infiltration      | 4   | Superficial haemorrhage     | 41  |
| Optic Nerve infiltration                   | 1   | Deep intraretinal haemorrhage| 29  |
| Papilloedema                               | 4   | White centred haemorrhage   | 16  |
| Choroidal infiltration (Exudative RD)      | 2   | Dilated and tortuous veins  | 12  |
| Cotton wool spots                          | 7   | Subhyaloid haemorrhage      | 4   |
| Subhyaloid haemorrhage                     | 4   | Vitreous haemorrhage        | 2   |
| Vitreous haemorrhage                       | 2   | Disc haemorrhage            | 4   |
| Disc haemorrhage                           | 4   | Sub conjunctival haemorrhage| 12  |
| Sub conjunctival haemorrhage               | 12  | Macular edema               | 3   |
| Macular edema                              | 3   | Uveitis                     | 2   |
conjunction with Acharya Tulsi Regional Cancer Centre. One hundred and ten subjects diagnosed with Acute leukemia at Acharya Tulsi Regional Cancer Centre, Bikaner were enrolled in this study. The diagnosis of leukemia was based on history, clinical features, examination of blood film and bone marrow aspiration. Patients with diabetes, hypertension, primary ocular diseases, dense cataractous changes and other media opacities were excluded from the study. Subjects not giving an informed consent, unwilling for a complete eye examination or were too sick to be examined were also excluded. All patients underwent detailed examination of anterior and posterior segment which included Snellen’s best corrected visual acuity, slit lamp examination, intraocular pressure measurement by Applanation tonometry, posterior segment examination under pharmacological mydriasis using direct, indirect ophthalmoscopy and slit lamp biomicroscopy using Volk 78D lens. Fundus photography documentation was done in cases with positive finding. A proforma was devised to include patient’s demographic data, brief medical and treatment history, anterior and posterior segment examination and detailed haematological and radiological investigations.

Results
The study subjects comprised 57 males and 53 females whose age ranged from 22 months to 58 years. There were 44 adults and 66 children. Out of total 110 diagnosed cases of leukemia enrolled in the study, 64 subjects (58.18%) had Acute Lymphoblastic Leukaemia and 46 patients (41.82%) (Graph1) were of Acute Myeloblastic Leukaemia. Ocular lesions were found in 61 subjects (55.45%). Twenty nine subjects (63.04%) of the Acute Myeloid Leukemia (n=46) and 32 (50.0%) (Graph 2) of acute lymphoid leukemias (n=64) had ophthalmic manifestations of leukemia (p<0.004). Primary or direct leukemic infiltration was seen in 11 (10%) patients. Of the 11 patients with direct leukaemic manifestations, 8 (72.73%) had AML and 3 (27.27%) had ALL. Secondary or indirect involvement due to anemia, thrombocytopenia, hyperviscosity, and immunosuppression were seen in 60 (54.54%) patients. Of these 60 patients, 28 were AML (46.67%) and 32 (53.33%) were ALL. (p<0.001) Of the 44
adult leukemic patients, 30 (68.18%) had leukemia related ocular changes while 31 (46.97%) of 66 children with leukemia had leukemic opthalmopathy. Thirty four (59.65%) males and 27 (50.94%) females had ophtalmic manifestations of leukemia (Graph 3). Ninety four (85.45%) subjects were undergoing chemotherapy while 16 (14.55%) subjects were not undergoing any form of treatment prior to ophthalmic evaluation. Of these subjects, 54/94 (57.45%) who had chemotherapy had changes while 7/16 (43.75%) of those who did not have chemotherapy had changes. Eight patients out of 110 (7.27%) had opthalmic manifestation on presentation. Leukemic opthalmic involvement was symptomatic in 38 (62.29%) and asymptomatic in 23 (37.71%) of subjects.

Discussion
Knowledge of ocular involvement in leukemia is important because the eye is the only site where the leukemic involvement of nerves and blood vessels can be directly observed. Ophthalmic involvement in leukaemia can precede the diagnosis of leukaemia or can occur during course of the disease or secondary to treatment. The reported prevalence of ocular involvement in leukaemia ranges from 9% to as high as 90%.

This divergent variation in results may imply the transient nature of leukeamic ocular findings, which may be waxing and waning with time and treatment. It may also be due to the varied study designs and study centres. It is estimated that up to 69% of all patients with leukaemia show fundus changes at some point in the course of their disease.

The 55.45% prevalence of leukemic ophthalmopathy documented in the present study is comparable to 69.0% reported by Alemayehu et al, but differed markedly from 35.4% reported by Reddy et al, and 39.0% in a series by Schachat et al. The observed disparity could be attributed to the difference in case mix between the present study and those of Reddy et al, and Schachat et al. In the present study, the spectrum of leukemic ophthalmopathy showed a preponderance of posterior segment over anterior segment manifestations. These resulted predominantly from secondary hematologic complications caused either by the leukemia itself or its treatment rather than primary leukemic ocular infiltration. Superficial and deep retinal hemorrhages were the leading posterior segment lesions while sub-conjunctival hemorrhage (Figure 2) was the commonest anterior segment sign observed in this study.

Conclusion
Leukaemic ophtalmic lesions were found in 55.45% of patients. Ocular involvement is more common in AML than in ALL. Secondary involvement of the retina is the most common ocular manifestation in leukemia. The ophtalmic manifestations of leukemia tended to involve more of the posterior than the anterior segment structures of the eye, and resulted more from secondary hematologic complications rather than primary leukemic infiltration. It is sometimes difficult for the physician to fully appreciate how frequently leukaemia involves the eye, probably because many patients remain asymptomatic in the earlier stages of ocular involvement. Numerous intra-ocular and extra-ocular changes may be rare, but can still be of prognostic significance. All leukaemia patients should have an ophtalmic assessment at diagnosis and periodically at least every 6 months as it could be a critical part of their follow-up and will guide the choice of therapeutic regimen. We suggest that full collaboration among physicians, oncologists, and ophthalmologists is needed, with prompt ophtalmic assessment of patients suspected to have eye manifestations.

References
1. Catovsky D. Chronic lymphocytic leukemias and other leukemias of mature B and T Cells. In: Weatheral DJ, Ledingham JC, Warell DA, editors. Oxford Textbook of Medicine. Oxford: Oxford University Press; 1996. pp. 3419–22.
2. Gordon KB, Rugo HS, Duncan JL, Irvine AR, Howes EL, O’Rein JM, et al. Ocular Manifestations of leukemia: Leukemic infiltration versus infectious process. Ophthalmology 2001;108:2293–300
3. Sharma T, Grewal J, Gupta S, Murray PL. Ophthalmic manifestations of acute leukemias: The ophthalmologist’s role. Eye (Lond) 2004;18:663-72.

www.djo.org.in
4. Reddy SC, Menon BS. A prospective study of ocular manifestations in childhood acute leukaemia. Acta Ophthalmol Scand 1998; 76:700-3.
5. Curto Mlo, Zingone A, Aguaviva A, Bagnulo S, Calcutti L, Cristiani L et al. Leukaemic infiltration of the eye: results of therapy in a retrospective multicentric study. Med Pediatr Oncol 1989; 17:134–9.
6. Ohkoshi K, Tsiaras WG. Prognostic importance of ophthalmic manifestations in childhood leukaemia. Br J Ophthalmol 1992; 76:651–5.
7. Singh AD. The prevalence of ocular disease in chronic lymphocytic leukaemia. Eye (Lond) 2003; 17:3-4.
8. Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. Surv Ophthalmol 1983; 27:211-32.
9. Leonardi NJ, Rupani M, Dent G, Klintworth GK. Analysis of 135 autopsy eyes for ocular involvement in leukemia. Ann J Ophthalmol 1990; 109:436-44.
10. Alemayehu W, Shamebo M, Bedri A, Mengistu Z. Ocular manifestations of leukaemia in Ethiopians. Ethiop Med J 1996; 34:217-24.
11. Reddy SC, Jackson N, Menon BS. Ocular involvement in leukemia – a study of 288 cases. Ophthalmologica 2003; 217:441-5.
12. Schachat AP, Markowitz JA, Guyer DR, Burke PJ, Karp JE, Graham ML. Ophthalmic manifestations of leukemia. Arch Ophthalmol 1989; 107:697-700.
13. Omoti AE, Omoti CE, Momoh RO. Ocular disorders in adult leukemia patients in Nigeria. Middle East Afr J Ophthalmol 2010; 17:165-8.
14. Guyer DR, Schachat AP, Vitale S, Markowitz JA, Braine H, Burke PJ, et al. Leukemic retinopathy. Relationship between fundus lesions and hematologic parameters at diagnosis. Ophthalmology 1989; 96:860–4.

Cite This Article as: Kochar S, Singhal Y, Manohar JM, Jain K. Ophthalmic Manifestations In Patients of Acute Leukaemia Presenting to A Tertiary Care Centre In Western Rajasthan.

Acknowledgements: Nil

Conflict of interest: None declared

Source of Funding: None

Date of Submission: 22 September 2017
Date of Acceptance: 6 December 2017

Address for correspondence

Shilpi Kochar MS
Assistant Professor
Department of Ophthalmology
S.P. Medical College, Bikaner, India
Email id: drshilpijain38@yahoo.com