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Prevalence Of Ocular Manifestation In Haematological Malignancies - A Clinical Study

[1]Liji Menon M.,[2]Elizabeth John,[1]Deepthi R., [2]Shaji A.
[1]*Department of Ophthalmology, M.O.S.C Medical College, Kolenchery.*
[2]*Department of Ophthalmology,Medical College Hospital, Kottayam.*
Corresponding Auhor: [1]Liji Menon M

Abstract: ***Background****: Ocular manifestation may be the primary indication of underlying haematological malignancy and are varied. Both high vascularity and unique vascular anatomy of eye play a role in the ocular manifestations of hematological diseases.Blood malignancies may present with ocular involvement or ocular manifestations may arise during the course of disease or during treatment.*
Objective:*To study the prevalence of ocular manifestation in patients diagnosed to have haematological malignancies in a rural medical college in South India over a period of 18 months.*
Methodology:*The study covered 100 patients who were diagnosed to have haematological malignancy of any type who attended the ophthalmology OPD directly or in other departments in the same medical college. Clinical evaluation including relevant history, specific ocular complaints, general and systemic examination and ocular examination were done. Patients with past history of ocular disease or documented ocular changes related to any chronic medical illness like diabetes mellitus, hypertension were excluded from the study.*
Results and Conclusion: *In the study 26% of patients were found to have ocular manifestation. Ocular involvement was more common in age less than 50(73%). Ocular involvement was mainly in AML (34.6%)followed by ALL(23%)and CML(19%).Anterior segment findings were seen in 34.6% and fundus findings in 69.23%.*
Key words: *Acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid and lymphoid leukemias (CML,CLL), multiple myeloma, lymphoma.*

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I. Introduction

Haematological malignancies encompass a wide spectrum of disorders that can present with ocular manifestations. Ocular manifestations may be the initial indication of any underlying haematological disorder. Haematological malignancies are neoplasms of haematopoetic system and is classified into leukaemia and lymphomas based on the cell type predominantly involved[1]. The eye can be involved by direct invasion of tissue, by neoplastic cells or manifestations, may be of associated haematological abnormalities like anaemia, thrombocytopenia or hyper viscosity states[2]. Leukaemia, shows ocular manifestation like Roth's spots, arteriolar attenuation, proptosis due to direct infiltration of ocular tissue or as an opportunistic infection or associated haematological abnormality.[3] Pathogenesis of retinopathy involves anaemia, haemorrhages diathesis, hypertension, tissue hypoxia and vascular stasis.Taking into consideration the advances made with regard to the treatment modalities, the number of survivors of this disease is ever increasing and more number of patients with intra ocular manifestation are likely to present to the ophthalmologist with various sequelae and complications. Knowledge of intra ocular manifestation of haematological malignancies is thus important because not only does the eye reflect the disease state of the body, but also these manifestations may be the initial mode of presentation of the systemic illness.[1]

II. Materials And Methods

The present study was conducted at Government Medical College Hospital Kottayam as a hospital based descriptive study over a period of 18months. Study was undertaken with the primary intention of finding the proportions of various ocular manifestations in haematological malignancies. 100 patients diagnosed to have haematological malignancies of any type who either attended the department of Ophthalmology directly or admitted in other departments like radiotherapy,paediatrics and general medicine were included in the study.

Study Design: Prospective observational study

Study Location: Hospital based clinical study involving departments of Ophthalmology,Radiothaerapy, Pediatrics and General Medicine at Government Medical college Kottayam,Kerala.

Study Duration:18 months

Sample size: 100 patients

Samle size: It was calculated using prevalence of ocular manifestation in haematological disorders of 50% by Kalpana et al, in a study done at Chennai. Sample size was found to be 100.

Study Procedure:A total number of 100 patients were studied. Clinical evaluation in each case included taking relevant history regarding time of diagnosis of malignancies, symptoms at diagnosis and any specific ocular complaints. Informed written consent was taken from each patient or guardian.
An overall general and systemic examination was done and significant findings like pallor and hepatosplenomegaly were noted. A thorough ocular examination was done in all patients **.**
The ophthalmic examination includes;

- Visual acuity
- External eye examination
- Ocular motility
- Pupillary reflexes
- Anterior segment examination by slit lamp microscopy
- Dilated examination by direct and indirect ophthalmoscopy

Any relevant investigation available with the patient like blood investigation, bone marrow study, lymph node biopsy reports were noted. All cases were diagnosed clinically

Inclusion Criteria
Patients admitted in radiotherapy, pediatrics and general medicine who were diagnosed cases of hematological malignancies by peripheral smear, bone marrow or any other relevant investigations and cases diagnosed in ophthalmology department during routine evaluation of ocular symptoms.

Exclusion criteria
Patients with past history of any ocular disease or documented ocular changes related to any chronic medical illness like diabetes mellitus and hypertension.

Ethical Consideration
All the data will be kept confidential and will be assessed only by the investigator and authorized personnel.

III. Results

Study involved 100 patients diagnosed as cases of different haematological malignancies. Leukemias accounted for 88% cases. Among leukemias various haematological malignancies that were encountered during the period were AML (37%)followed by ALL(30%),CML (16%) andCLL(5%).Other hematological malignancies seen were Multiple myeloma (MM) (6%) and lymphomas of non hodgkins variety (NHL)(6%)(Table 1). Considering the sex distribution males were more involved (68%). (Figure 1)

Table no: 1: Distribution of Cases**.**

TYPE OF MALIGNANCIES	**PERCENTAGE OF CASES**
ALL	30
AML	37
CML	16
CLL	5
MM	6
NHL	6

Figure 1: Sex distribution**.**

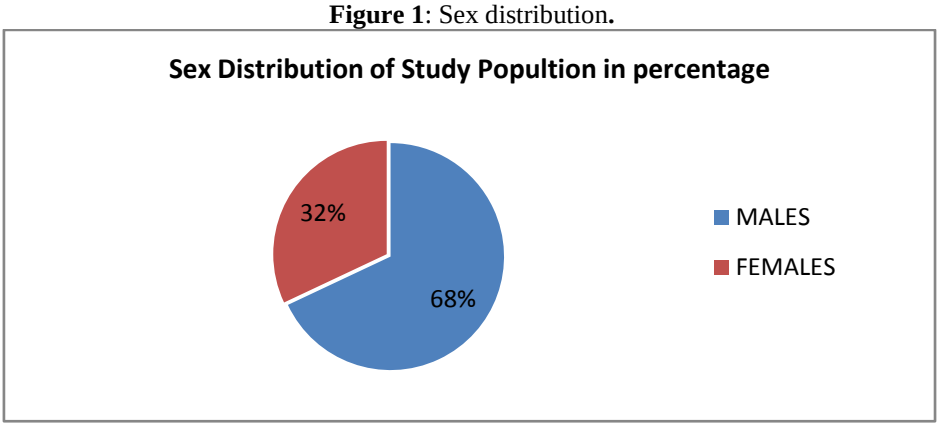
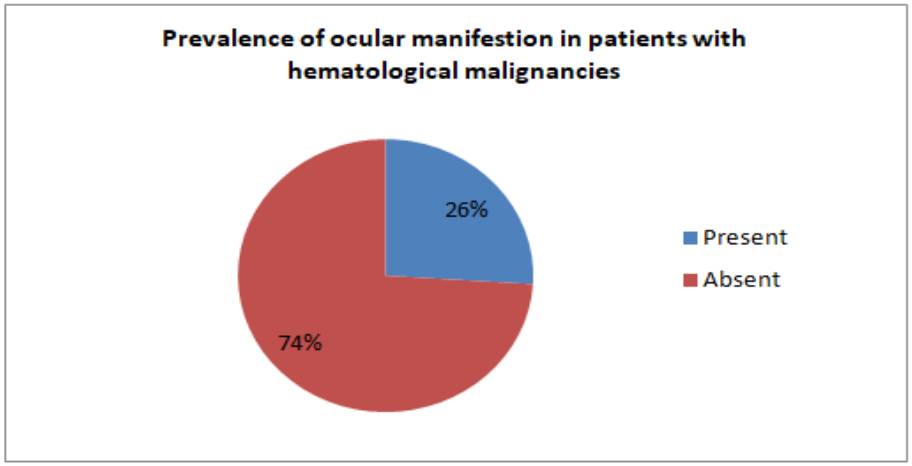


Figure 2:Prevalence of ocular manifestations



Among the 100 cases ,26 ,patients had ocular involvement. (Figure 2).Leukemias accounted for 76.9%cases with ocular findings of which AML accounted for majority of cases with ocular findings (34.6%)followed by ALL (23%) and CML (19%). No ocular findings were seen in cases of CLL. Among non leukemic varieties multiple myeloma had 15%cases with ocular findings and non hodgkins lymphoma (7.6%) (Figure 3).Among the 26 cases with ocular involvement, maximum number of patients were in 40-50 age group. 19 cases were of less than 50 age group.(figure 4)Among 67 cases of adults 28.3% had ocular manifestations. Out of 33 pediatric cases 21%had ocular manifestations . Lesser number of patients with ocular involvement in paediatric age group could be attributed to a difficulty in fundus examination.

Figure 3: Ocular Manifestation In Different Type Of Haematological Malignancies**.**

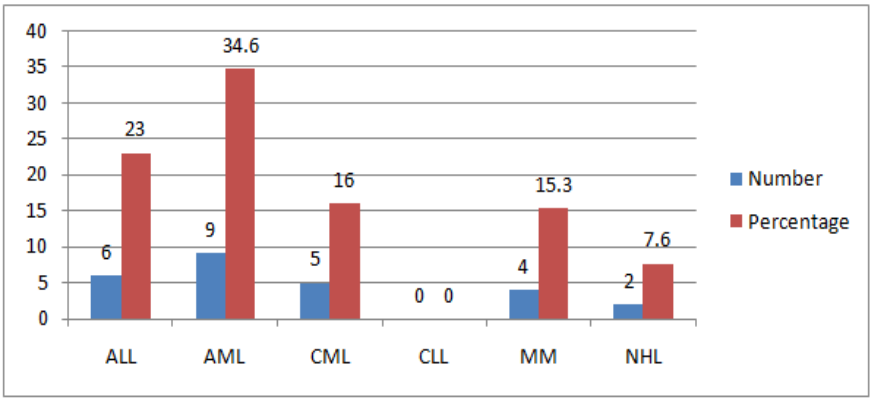
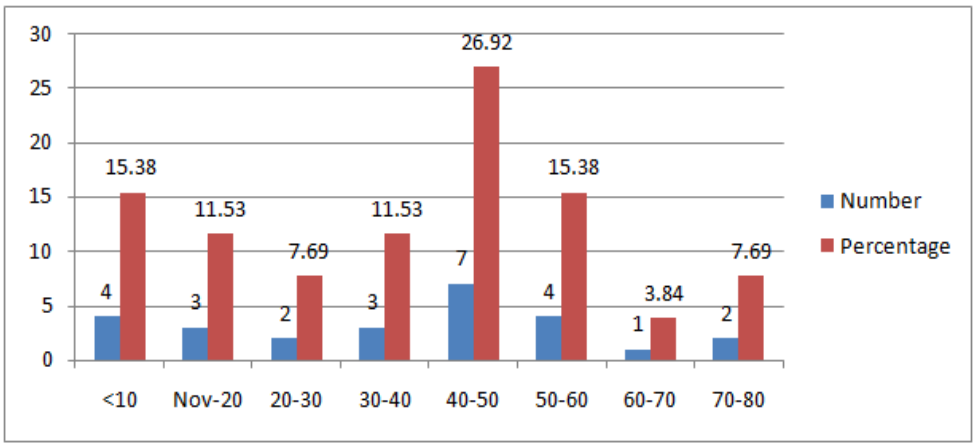


Figure 4: Age Distribution (Cases With Ocular Involvement **)**



Out of 26 cases,18 cases were bilateral(69.23%). Anterior segment involvement were seen in 9 cases (34.61%). (Table 2).Neuroophthalmicinvolvement were seen in 4 cases (15.3%) in the form of sixth and seventh nerve palsy &optic disc involvement(Table 3). Posterior segment involvement were seen in 18 cases (69.23%).)Retinal hemorrhages accounted for majority of findings. Both intraretinal and preretinal hemorrhages (57.63%)followed by venous dilatation & tortuosity (Table 4) .Retinal hemorrhages were seen in patients with low Haemoglobin and low platelet count. Mean haemoglobin andplatelet count in patients with and without retinal hemorrhages were found to be statistically significant (Table 5).Direct involvement was seen in 61.53% of cases. It was attributed to optic disc infiltration,perivascular sheathing and infiltration of anterior segment. Secondary involvement was due to anemia,thrombocytopenia and hyperviscosity.

Table No:2: Pattern Of Ocular Involvement- anterior segment manifestations

Proptosis	4
Mass Lesion In Eyelids	2
Conjunctiva (Sch)	2
Cornea	Nil
Pseudo Hypopyon	1
Neuro Ophthalmic Manifestations	4

Table 3: Neuro Ophthalmic Manifestations.

6th NERVE PALSY	**7th NERVE PALSY**	**OPTIC NERVE HEAD INFILTRATES**	**TOTAL**
1	1	2	4

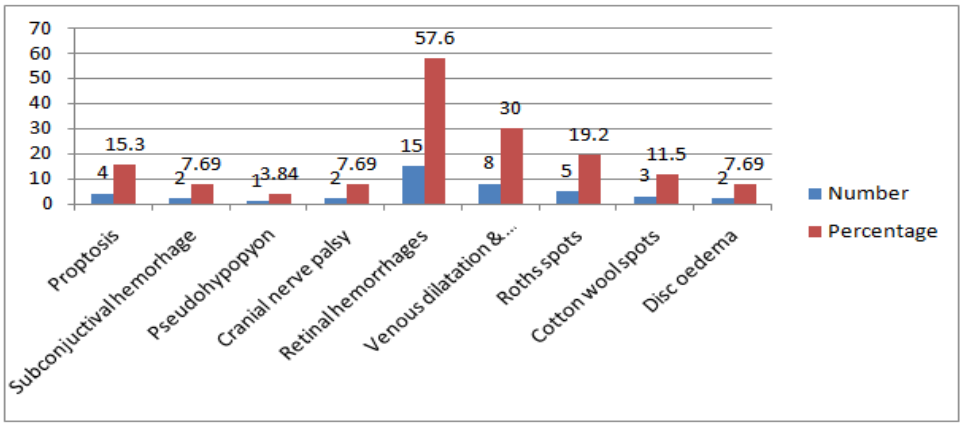
Table 4: Posterior Segment Findings.

TYPE	**VD & T**	**IRH**	**CWS**	**ROTH'S SPOT**	**PRH**	**DISC EDEMA**
ALL	2	1		1		2
AML	2	5	2	3	3	
CML	4	3	1	1	2	
MM	-	-	-	-	1	
LYMPHOMA	-	-	-	-	-	
TOTAL (26)	8	9	3	5	6	2
PERCENTAGE	30.7%	34.61%	11.5%	19.2%	23.02%	7.69%

Table 5: Comparison of mean hemoglobin and platelet count in patients with and without retinal hemorrhages

			Mean value in cases with hemorrhages	Mean value in cases without hemorrhage	P value
Retinal hemorrhages	Intraretinal hemorrhage	Hemoglobin	7.02	9.84	0.023
		Platelet count	46000	112000	0.019
	Preretinal hemorrhage	Hemoglobin	6.59	8.92	0.017
		Platelet count	34800	124850	0.014

Figure 5: Ocular Manifestation InHaematological Malignancies.



IV. Discussion

During the study period of 18 months, 100 patients diagnosed as having different hematological malignancies admitted to medical, radiotherapy, pediatric wards and attending the ophthalmology department were studied with regard to any manifestation involving the eye.

Various hematological malignancies that were encountered during the study period were leukemia including acute lymphatic leukemia (ALL) , acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphatic leukemia (CLL), multiple myeloma (MM) and lymphomas of non hodgkins variety (NHL).Out of 26 cases of hematological malignancies, 18 cases were bilateral (69.23%), 16 out of 20 cases of leukemias were bilateral (80%).

The broad finding indicated that 26 out of the total 100 had ocularmanifestation. The findings are comparable to that of similar previous studies. Schachatet. al.[4](1989) studied 120 patients of different haematological malignancies and reported 34% as having ocular involvement. Kareshet.al.[5] (1988) studied 56 newly diagnosed cases of leukaemia and reported ocular manifestations in 20 cases (34.71%). Retrospective study on leukemia at King Abdelaziz University Hospital, Jeddah by Badeebet. al.[6] spanning 10 years between june 1983 to may 1993 reported 41 cases out of which 11 had ocular manifestations.

Among the patients with ocular involvement maximum number were in the 40-50 years age group (26.92%). 19 cases were less than 50 years of age. Out of 33 pediatric cases, 7 had ocular involvement (21.3%). All pediatric cases were leukemias. Ridgeway et. al.[7] (1978) reported that 9% children with leukemia had ocular involvement whereas Ohkashi and Tsariaset. al.[8] (1992) reported 21.6% of ocular involvement in pediatric cases. In this study, percentage of leukemia children with ocular involvement is higher than the reported first study and comparable with the second study.

Direct leukemia infiltration can be in form of optic disc infiltration, retinal infiltration, perivascular sheathing infiltration of anterior segment which can masquerade as uveitis and localized granulocytic sarcoma or chloroma in case of myeloid leukemia .Eye can be secondarily involved with manifestation of anemia , thrombocytopenia and hyper viscosity. In this study 5 cases had secondary ophthalmic manifestation without primary infiltration.Among the 26 cases with ocular findings, anterior segment was involved in nine cases.

Neuroophthalmic involvement were seen in four cases (1 ALL, 2 AML , 1 MM) amounting to 15.38% of cases with ocular involvement. Among these one were cases of sixth nerve and seventh nerve palsies.. One patient with AML had relative afferent pupillary defect (RAPD)(LE) with fundus showing hemorrhages, cotton wool spots and Roth's spots. She had presented with acute blurring of vision. Optic disc was oedematous. Another patient with AML had RAPD (RE) with optic disc edema in both eyes.Badeedet.al. reported 3 patients

with cranial nerve palsy (one seventh, one Sixth and one third) secondary to CNS infiltration out of 17 cases studied.[5]

18 out of 26 cases with ocular involvement had findings in fundus (69.23%). Duke elder noted, retina is most commonly involved in leukemia complication. Allen and Straatma stated that most destructive clinical alterations in leukemias were noted in retina[2].

The commonest finding in the fundus was intra retinal hemorrhage, mostly superficial flame shaped hemorrhages and less commonly deep dot retinal hemorrhage. Nine out of 26 cases with ocular involvement had intraretinal hemorrhage (IRH).Jackson et al[9](1997) reported that macular hemorrhage in adult acute leukemias is a highly significant risk factor for development of subsequent intra retinal haemorrhage. Jackson and Reddy in 2004 reported IRH as the commonest retinal lesion, which was seen in 40% of patients which is quite comparable to present study(34.61%). Culler et al[10] was unable to correlate between blood profile and retinal pathology but the study haemorrhage occurred most frequently in patients with low hemoglobin and low platelet count. (Mean Hemoglobin = 7.02, Mean PLC = 46,000), p=0.023.

Venous dilatation and tortuosity (VDT) was the next common fundus finding seen . Eight out of 26 cases had VDT. This was a bilateral finding in all cases and probably reflects the hyper viscosity of circulation in leukemias. White centered hemorrhages or Roth's spots were seen in 5 cases (19.2%) with ocular involvement. Roth's spots are most frequently encountered in AML indicating the acuteness and infiltrative nature of this form of leukemia. Schachat et al reported 13 cases of Roth's spot in 120 patients studies [4](11%)[2]. Cotton wool spots were seen in three cases of leukemia with ocular involvement (11.5%). Schachat et al reported 19 cases out of 120 patients had cotton wool spots [4](16%)[2].There were 2 cases of ALL with papilloedema with a disc edema of 2 diopters in 1 case and other had optic nerve head infiltration (direct) with marked disc edema, pallor of disc , blurring of margins and had prominent telengiectatic vessels around the disc.Kincaid and Green reported that 18% of acute leukemias and 16 % of chronic leukemias had some form of optic nerve involvement.[3]

V. Conclusions

Ocular manifestations were found in 26% of patients with haematological malignancies and the findings are mostly bilateral. Ocular involvement was more common in less than 50 years of age.Regarding the pattern of ocular involvement , direct involvement of the eye in form of leukemic deposits seen in 42.3%, Roth's spots in 19.23% and secondary involvement due to anemia and thrombocytopenia in 46.185%. Among the ocular findings, lid, adnexal and anterior segment involvement was seen in 34.61% of which proptosis was the main finding.Ophthalmic fundus involvement was seen in 69.23% of which retinal hemorrhages was the commonest, which was almost bilateral. Occurrence of retinal hemorrhages statistically correlated well with low hemoglobin and low platelet count.

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Ethical approval: The study was approved by Institutional Ethical Committee.

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