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Original Research Article

STUDY OF OCULAR MANIFESTATIONS IN LEUKEMIA: A CROSS-SECTIONAL STUDY

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Abstract

Background: Several studies in literature have inferred that patients can have ocular symptom as the initial symptom of leukemia. Ocular involvement in leukemia can precede the diagnosis of leukemia, can occur during the course of the disease or be a sequel to therapy with steroids, chemotherapy or total body irradiation. To study various ophthalmic manifestations in leukemic patients, to know the frequency of ocular symptomology as the initial presentation in leukemic patients and to assess the incidence of ocular relapse in leukemic patients. **Materials and Methods:** Complete ophthalmic examination was performed in 50 patients of all age groups and in either sex diagnosed with leukemia of any stage, attending the Tertiary care Institute of India, for the duration of 2 years. **Result:** Among 50 cases of leukemias, 30 cases were of ALL (60%), 14-AML (28%), 1- CLL(2%) and 5- CML(10%). Ocular manifestation were present in 20 cases (40%), among these ALL being the commonest subtype (75%), younger age group(< 20 years) accounting for 65% and 70 % had ocular symptoms. Posterior segment involvement was seen in 15 cases(75%) of which, intraretinal hemorrhage being the commonest finding(60%) and anterior segment involvement was seen in 5 cases(25%), of which subconjunctival hemorrhage (60%) was commonest. None of the leukemic patients had ocular symptomology as their initial presentation. One patient (2%) had ocular relapse of ALL in form of iris nodule. **Conclusion:** Leukemia of acute form have more ophthalmic manifestation than chronic forms and generally affecting younger age group, hence early detection and appropriate management will lead to better clinical outcome.

INTRODUCTION

Leukemias are diffuse clonal neoplastic disorder of the bone marrow and blood cells. They are classified into myeloid or lymphoid based on their origin and into acute and chronic depending on the clinical course. Chronic leukemias arise from lymphocytic (chronic lymphocytic leukemia, CLL) or myeloid (chronic myelocytic leukemia, CML) precursor cells.[1] They are different from acute leukemias in that the morphology of the cell lines show marked differentiation and are divided into acute lymphocytic leukemia (AML), acute myelocytic leukemia (AML). The eye can be involved in leukemia by direct invasion of tissue by neoplastic cells or manifestations may be of associated hematological abnormalities like anemia, thrombocytopenia or hyper viscosity states or by opportunistic infections.[2] In leukemia there can be involvement of orbit, lids, adnexa, anterior segment and posterior segment of the eye. Taking into consideration the advances made in the treatment modalities of leukemia, the number of survivors of this disease is increasing and hence more and more patients with intraocular manifestation are likely to present to the ophthalmologist with various sequelae and complications. Leukemic patients may not have any ocular symptoms but on ophthalmic examination may show damage to ocular structure, ocular disorder have been reported in 30-90% of cases with leukemia.[3] Several studies in literature have inferred that patients can have ocular symptom as the initial symptom of leukemia.2 Ocular sanctuary is a well known but very rare form of relapse in leukemic patients, its occurrence is associated with poor prognosis.[4] The presence of leukemic infiltrates appears to correlate with central nervous system involvement and decreased survival.[5] Ocular involvement in leukemia can precede the diagnosis of leukemia, can occur during the course of the disease or be a sequel to therapy with steroids, chemotherapy or total body irradiation.[2] Ocular and orbital lesions have been reported to be the third most frequent extramedullary location of acute leukemias after the meninges and testicles.[3] Knowledge of intraocular manifestations is important because not only does eye reflect the disease state of the body, but also this

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manifestation may be initial mode of presentation of systemic illness. So early diagnosis and management can reduce the complication and restore the vision.[6] Present study was done with following Objectives: To study various ophthalmic manifestations in leukemic patients, to know the frequency of ocular symptomology as the initial presentation in leukemic patients and to assess the incidence of ocular relapse in leukemic patients.

MATERIALS AND METHODS

This cross-sectional Study comprised of 50 patients of all age and any sex diagnosed with leukemia of any stage, admitted in pediatric, medical oncology ward, hematology wards. Patients attending ophthalmology outpatient department at the Tertiary care Institute of India for the duration of 2 years were recruited in the study.

Inclusion Criteria

Patients of all age and any sex diagnosed with leukemia of any stage.

Exclusion Criteria

- Patients of leukemia who had any previous ocular diseases, or have undergone ocular surgeries.
- Leukemic patients with associated co morbidities like diabetic, hypertension etc. –
- Patients suffering from infectious disease.
- Patients with haematological disorder other than leukemia.

Patients were selected according to inclusion and exclusion criteria. Diagnosis of leukemia was based on clinical information, cytological features of well stained peripheral blood smear, bone marrow aspiration cytology and biopsy, haematological parameters. Informed consent from the patient was taken. Detailed general and ocular history was recorded. General physical examination done which included consciousness, orientation, pallor, icterus, cyanosis, clubbing, lymphadenopathy, edema, temperature, pulse rate, respiratory rate, blood pressure. Systemic examination included, central nervous system, cardiovascular system, respiratory system and per abdomen.

Ocular Examination

- Head posture
- Facial symmetry
- Extraocular movements
- Best corrected visual measured on snellens chart, if patients could not read the chart, the ability to count fingers at varying distances to perceive hand movements or light was determined and recorded.
- Slit lamp evaluation for lids, adnexa and, anterior segment
- Measurement of intraocular measurement by applanation tonometry/schiotz tonometry in sick patients
- Fundus examination was done after complete mydriasis by direct ophthalmoscope, indirect ophthalmoscope (with 90 D and 20D Lens).

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS

Out of 50 leukemia cases, 30 were that of Acute lymphatic leukemia (ALL), 14 - Acute myeloid leukemia (AML), 1 - Chronic lymphatic leukemia (CLL), 5 - Chronic myeloid leukemia (CML). [Table 1] Out of 50 cases, 38 (76%) were males and 12 (24%) were females. [Table 2] 20 cases (40%) out of 50 cases had ocular manifestation of which ALL accounted for 15 number of cases (50%)), AML- 4 cases and CML-1 case. [Table 3] Out of 50 cases, age group between 0-10 years accounted for 19 cases (38%) with leukemic disease, followed by age group between 11-20 years which accounted for 13 (26%) cases.

Among the 20 cases with ocular manifestations, age group between 11-20 accounted for 7 cases (35%), followed by age group 0-10 years accounted for 6 (30%) cases and the remaining 6 cases were above 20 years. [Table 4] Blurring of vision accounted for -22%, followed by redness of eye -6% and asymptomatic 72%. Out of 20 cases with ocular manifestation, 65% of patients had ocular manifestations within 6 months of diagnosis of disease, rest developed within 1 year. Anterior segment accounts for 25% of total ocular manifestation cases, ALL accounts for maximum number -4 cases (80%) with anterior segment manifestation.

15 out of 20 ocular manifestation cases had fundus changes, which accounts for 30% of total cases and 75% of patients with total ocular manifestations. [Table 5] ALL cases accounting for maximum number of cases with fundus changes (11 cases), AML-3 cases and CML-1 case. IRH is commonest finding in fundus and involving 9 number of cases, followed by RS (4 cases). [Table 6] Bilateral involvement was seen in 65% of patients with ocular manifestations and unilateral 35%. ALL accounting for total 10 cases of bilateral involvement of eye.

Table 1: Distribution of Different Types of Leukemia in Study Group

Type	Incidence	Percentage
ALL	30	60
AML	14	28
CLL	1	2
CML	5	10
Total	50	100

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Table 2: Frequency of Disease among Male and Female.

Sex	No of patients	%
Male	38	76.0
Female	12	24.0
Total	50	100.0

Table 3: Frequency of ocular manifestations in leukemic subtypes.

Diagnosis		Ocular manifestation		Total
		Absent	Present	
ALL	Count	15	15	30
	% within Diagnosis	50.0%	50.0%	100.0%
AML	Count	10	4	14
	% within Diagnosis	71.4%	28.6%	100.0%
CLL	Count	1	0	1
	% within Diagnosis	100.0%	0.0%	100.0%
CML	Count	4	1	5
	% within Diagnosis	80.0%	20.0%	100.0%
Total	Count	30	20	50
	% within Diagnosis	60.0%	40.0%	100.0%

Table 4: Age Distribution with Ocular Manifestations

Age (years)		Diagnosis			Total
		ALL	AML	CML	
0-10	Count	6	0	0	6
	% within age	100.0%	0.0%	0.0%	100.0%
11-20	Count	6	1	0	7
	% within age	85.7%	14.3%	0.0%	100.0%
21-30	Count	0	2	1	3
	% within age	0.0%	66.7%	33.3%	100.0%
31-40	Count	1	1	0	2
	% within age	50.0%	50.0%	0.0%	100.0%
41-50	Count	1	0	0	1
	% within age	100.0%	0.0%	0.0%	100.0%
51-60	Count	1	0	0	1
	% within age	100.0%	0.0%	0.0%	100%
Total	Count	15	4	1	20
	% within	75.0%	20.0%	5.0%	100.0%

Table 5: Frequency of fundus involvement in Leukemia

Diagnosis		Fundus		Total
		Absent	Present	
ALL	Count	4	11	15
	% within Diagnosis	27.0%	73.0%	100.0%
AML	Count	1	3	4
	% within Diagnosis	25.0%	75.0%	100.0%
CML	Count	0	1	1
	% within Diagnosis	0.0%	100.0%	100.0%
Total	Count	5	15	20
	% within Diagnosis	25.0%	75.0%	100.0%

Table 6: Fundus Findings in Leukemia

TYPE	VDT	IRH	CWS	RS	PRH	SH	DISC	Macula	Retinal edema	DRI
ALL	2	7	1	2	0	0	1	1	2	1
AML	1	1	1	1	1	0	1	0	0	0
CML	0	1	1	1	0	0	0	0	0	0
TOTAL	3	9	3	4	1	0	2	1	2	1

DISCUSSION

During the study period, 50 patients diagnosed as having leukemia, admitted to the medical, pediatric oncology and hematology wards, patients attending the ophthalmology outpatient departments during the study period were studied with regard to any manifestations of the leukemic process involving the eye, to assess the frequency of ocular symptomology as the initial presentation in leukemic patients, and to assess the incidence of ocular relapse in leukemia.

Out of 50 leukemia cases, 30 were that of Acute lymphatic leukemia (ALL), 14 - Acute myeloid leukemia (AML), 1 - Chronic lymphatic leukemia (CLL), 5 - Chronic myeloid leukemia (CML). Out of 50 cases, 38 were male and 12 were female. 20 cases out of 50 cases had ocular manifestation. Karesh etal studied newly diagnosed, untreated patients with AML alone and reported ocular manifestations in 28 cases (53%).[7,8] Retrospective study on leukemia at King Abdulaziz university hospital, jeddah by Badeed etal spanning 10 years between June 1983 to may 1993 reported 31 cases out of which 17 had

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ocular manifestations(55%). Previous studies have described an overall ocular involvement in 9-90% of cases with leukemias based on clinical examination or autopsy finding.[6,9] Ocular involvement in CLL is uncommon a reflection of the indolent course of CLL as compared to other leukemias.[10] Present study also infers ocular manifestation being more common in acute leukemias. Among the 20 cases with ocular manifestations, age group between 11-20 accounted for maximum number that is 7 cases, followed by age group 0-10 years accounted for 6 cases and the remaining 6 cases were above 20 years. Ridgeway et al reported that 9% of children with acute leukemia had ocular manifestation where as ohkashi and tsiaras et al reported 21.3%.[11]

In the present study none of the patients had ocular symptoms as the initial presentation in leukemic patients. Dutschke etal reported a single case of ALL with visual impairment as the initial symptom and the fundus demonstrated bilateral macular pre retinal hemorrhage.[12] Badeeb et al reported 8 patients out of 17 patients had leukemic ophthalmopathy as the initial diagnosis of disease.

Among 20 cases majority of patients had ocular manifestations within first 6 months of diagnosis, rest developed within 1year. Thus in this study it is evident that ocular involvement in leukemia is seen quite early in course of disease. Badeeb et al,[13] reported that the interval between the diagnosis of leukemia and first ocular manifestations was 6 months in 11 patients and 24-60 months in 6 patients out of the 17 patients with ocular involvement.[14]

Among 20 cases of ophthalmic manifestations, anterior segment was involved in 5 cases (25%) were of ALL and 1 from AML, rest of all had fundus changes that is 15 cases (75%). There were 5 cases with anterior segment findings seen during study period, which corresponds to 25% of patients with total ocular manifestations.

Three patients had subconjunctival hemorrhages, one patient who was case of ocular relapse in ALL, had iris nodule on examination, for which paracentesis was done and diagnosis confirmed by iris biopsy. Rothova et al identified 40 patients with uveitis masquerade syndrome of which 3 had intraocular leukemia.[15] In present study anterior segments findings accounted for 25% of total ocular manifestation cases. These may have been resulted predominantly from secondary hematological complications caused either by systemic leukemia or its treatment rather than primary leukemic infilteration.[2,3]

15 out of 20 ocular manifestation cases had fundus changes, which accounts for 30% of total cases and 75% of patients with total ocular manifestations. Allen and Straatsma stated that the most destructive clinical alteration in leukemia was noted in retina.[16] Jackson and Reddy studied 127 cases of acute leukemia and 42% had retinal changes.[17]

There were 9 cases with intraretinal hemorrhages, which was commonest finding in fundus, most of them being superficial flame shaped, 9 out of 20 cases had IRH, 5 of these cases had IRH as sole ocular manifestation which amounts for (all were ALL) 55.5% of total cases. The rest were associated with other ocular findings. Presenting symptoms were in 3 cases (33% of total 9 cases) and 6 (66.6% of total 9 cases) cases had no presenting symptom, so majority of cases with intraretinal hemorrhages had no symptoms. Most commonly hemorrhages were seen in posterior pole that is around disc and macula.

IRH in different types of leukemias:

- ALL-7 cases (88.88%)
- CML-1 case (11.1%)
- AML-1case (11.1%)

Jackson and Reddy,[17] study reported IRH as the commonest retinal lesion, which is comparable to present study. Culler et al,[18] was unable to correlate between blood profile and retinal pathology, but did note that the hemorrhage occurs most frequently when RBC count was extremely low, when platelet count was extremely low, when platelet count was comparatively low in AML.

There was 2 cases with disc edema that is 4% of total number of cases, 1 case was ALL and other was AML, in both cases it was bilateral involvement of eye. The patient with ALL had history of sudden blurring of vision since 1 day, on examination there was disc edema with edema of only central retina including macula. The other case of AML had history of blurring of vision since 1 week, on examination had only disc edema, involving both eyes, which was due to raised intra cranial tension. Optic disc edema is usually bilateral and due to raised intracranial pressure secondary to mass effect associated with blood dyscrasia (meningial infiltration, granulocytic sarcoma) it is also due to serum hyper viscosity.19 Kincaid and green6 (pathological study) reported that 18% of acute leukemia and 16% chronic leukemic patients had some form of optic 46 nerve involvement. Allen and Stratsma,[16] reported that 13% of leukemic patient had some form of optic nerve involvement. Badeed,[13] reported optic nerve involvement in 7 patients with leukemia.

Two cases had retinal edema, both were of ALL group, both the patients had history of sudden blurring of vision since 1 day, one patient was 10 years old, fundus showed central retinal edema, disc and macula was also involved as mentioned earlier, the other patient of adult age group had retinal edema but disc was spared, edema occurs due to hyperpermeable or leaky retinal capillaries.[19]

One case of ALL had diffuse retinal infiltrates, this patient had history of bilateral blurring of vision since one day, on examination bilateral fundus showed diffuse massive retinal infiltrates because of which disc, macula and other fundus details could not be made out. Schachat and co-workers found 4 patients (3%) with leukemic retinal infiltrate. Allen and Strasstma found much higher incidence of leukemic retinal infiltrate in eyes of patients with acute leukemia (80%).[16]

In this study one patient of ALL who was about to complete the chemotherapy treatment and was in

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maintenance phase, showed iris nodules in one eye on ophthalmic examination, for which paracentesis was done, iris biopsy taken and diagnosis was confirmed, it was a case of iris relapse in leukemia. Patient at the end of one year underwent bone marrow stem cell transplant and he died after one year of transplant. The anterior segment is an uncommon site of extramedullary relapses in the large published series and is seen most frequently in ALL.[20] Ocular infiltration by direct invasion of leukemic cells is associated with CNS relapse.[21]

ALL-Out of 30 cases,15 had ocular manifestation and out of it 11 cases had fundus changes (73%), 4 had anterior segment changes. Therefore it can be inferred that ALL has significant tendency to produce fundus changes. AML- out of 14 cases, 4 had ocular manifestation, of which 3 cases (75%) had posterior segment involvement and 1 case with anterior segment involvement. Thus in this study, AML also showed significant fundus changes. CLL: The single case of CLL was seen in 48 year old female, with no ophthalmic findings. CML: There were total 5 cases, ocular involvement was present in 1 case showing fundus changes.

Acute Leukemias

Among the 44 cases, ocular manifestation was present in 19 cases, of which anterior segment manifestation was in 5 cases and posterior segment in 14 cases

Chronic Leukemias

Among the 6 cases, 1 case had ocular involvement which involved posterior segment showing intraretinal haemorrhage, cotton wool spots and roth spots. This study infers that incidence of acute leukemias is higher than chronic and ocular manifestations are significantly high with acute leukemia.

CONCLUSION

Leukemia is a malignant disorder of white blood cell precursors. The acute forms are more serious and generally affect children. Ocular involvement in leukemia has been described in 9-90%. Asymptomatic patients account for 12% of total cases and in young children change in visual behavior can be overlooked leading to delay in diagnosis. Ocular manifestation were seen early in the course of the disease, hence early diagnosis and appropriate management will lead to better clinical outcome.

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