Original Article

Ophthalmic manifestations of acute and chronic leukemias presenting to a tertiary care center in India

Jacob Koshy, M Joseph John[1], Satish Thomas, Gurvinder Kaur, Nitin Batra, Wilson J Xavier

Context: Screening for ocular manifestations of leukemia, although not a routine practice, is important as they may antedate systemic disease or form an isolated focus of its relapse. **Aims:** This study evaluates the spectrum of ocular manifestations in acute and chronic leukemias presenting to a tertiary care center in India. **Settings and Design:** Subjects of leukemia presenting to a tertiary care center in India. **Subjects and Methods:** A prospective, cross-sectional study looking at the spectrum of ocular manifestations in all inpatients of acute or chronic leukemia. **Statistical Analysis Used:** The collected data were analyzed using the Statistical Package for Social Sciences for Windows software, version 16 (SPSS Inc., Chicago, Illinois, USA). **Results:** The study subjects (n = 96) comprised 61 males and 35 females whose age ranged from 18 months to 91 years (mean = 39.73, ±22.1). There were 79 adults and 17 children, 53 new and 43 existing patients, 68 acute and 28 chronic, 61 myeloid and 35 lymphoid patients. Ocular lesions were found in 42 patients (43.8%). The ocular manifestations of leukemia were significantly (P = 0.01467) more frequent in acute 35/68 (51.9%) than chronic 7/28 (25%) leukemias. Primary or direct leukemic infiltration was seen in 8 (8.3%) subjects while secondary or indirect involvement due to anemia, thrombocytopenia, hyperviscosity, total body irradiation, and immunosuppression were seen in 42 (43.8%) subjects. Ocular changes were present in 37/79 (46.8%) adults and 5/17 (29.4%) children (P = 0.09460). Twenty-eight males (28/61) 45.9% and 14/35 (40%) females had ocular manifestations (P = 0.2874). The ocular manifestations were significantly (P = 0.01158) more frequent in myeloid leukemias 32/61 (52.9%) than lymphoid leukemias 10/35 (28.6%). **Conclusions:** Leukemic ophthalmic lesions were found in 42/96 (43.8%) patients. Ocular involvement is more often seen in adults, acute and myeloid leukemias. All the primary leukemic manifestations were seen in males. A periodic ophthalmic examination should be mandatory for all leukemic patients, as ocular changes are often picked up in asymptomatic patients.

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Leukemia is a malignant proliferative disorder of hematopoietic bone marrow stem cells characterized by overcrowding of the bone marrow by immature neoplastic leucocytes and widespread infiltration of organs, tissues, and peripheral blood by immature leukocytes.[1] Ocular involvement in leukemia has long been recognized, and virtually every ocular tissue may be affected. The reported prevalence of ocular involvement in leukemia ranges from 9% to as high as 90%.[2,3] Ocular involvement in leukemia can precede the diagnosis of leukemia or can occur during the course of the disease.[4]

The ophthalmic manifestations of leukemia could result from primary/direct leukemic infiltration of ocular tissues or secondary/indirect ocular involvement following systemic leukemic changes. Primary leukemic infiltration can present in three patterns as anterior segment uveal infiltration; orbital infiltration including chloromas, spontaneous hyphema, orbital hemorrhages, and proptosis; and neuro-ophthalmic signs of central nervous system (CNS) leukemia that include optic nerve infiltration, cranial nerve palsies, and papilledema. The secondary changes are the result of hematological abnormalities of leukemia such as anemia, thrombocytopenia, hyperviscosity, or be a sequel to therapy with steroids, chemotherapy, bone marrow transplantation (BMT) or total body irradiation, and immunosuppression. These can manifest as retinal or vitreous hemorrhage, infections, and vascular occlusions.[5]

Retinopathy was earlier believed to be of no prognostic significance in acute leukemia.[6] However, now reports have demonstrated that the presence of ocular involvement is associated with poor prognosis in acute childhood leukemia.[7] Russo *et al*.[8] showed that in both acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL), the presence of specific orbital and ocular lesions was associated with a higher frequency of bone marrow relapses and CNS involvement, leading to a lower survival rate. The development of leukemic infiltrates in patients with leukemia mandates immediate systemic and neurological re-evaluation.[9] It is, therefore, important to consider an ophthalmic evaluation in all leukemic patients.

Departments of Ophthalmology and [1]Haemato-oncology and Bone Marrow Transplantation, Christian Medical College, Ludhiana, Punjab, India

Correspondence to: Dr. Jacob Koshy, Department of Ophthalmology, Christian Medical College, Ludhiana - 141 008, Punjab, India. E-mail: drjkoshy@gmail.com

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Late presentation in advanced stages of disease is common in African patients.[10] Considering the lack of medical resources for managing hematological malignancies outside the cities, this may be true of Indian patients as well. The pattern of ocular disease in Indian patients with hematological malignancies may thus be different from that reported in studies from more advanced countries. There is no literature available from the Indian subcontinent on the ocular findings in leukemic patients. Consequently, the investigators embarked on a cross-sectional assessment of the prevalence and pattern of leukemic ophthalmopathy among leukemic inpatients in a tertiary center in India. In addition to providing comparative data, the results would assist clinicians involved in leukemic care in optimizing care outcomes.

Aim

To study the spectrum of ocular manifestations in acute and chronic leukemias presenting to a tertiary center in India.

Subjects and Methods

All diagnosed leukemia patients admitted to the hematology, hemato-oncology, and BMT wards at a tertiary teaching hospital caring for patients with leukemia between January 2011 and December 2013 and were willing to participate in the study, were prospectively analyzed and included in this study. The diagnosis of leukemia was based on history, clinical features, examination of blood film, and bone marrow aspiration. Subdivision of leukemia into myelogenous and lymphocytic was made using cytomorphology and a combination of cytochemistry and immunophenotyping methods. Leukemia patients only presenting to the outpatient department were not included in the study. Subjects with systemic co morbidities such as diabetes and hypertension were also included, and ophthalmic manifestations due to these co morbidities were differentiated as best possible based on clinical examination. Subjects unwilling for a complete eye examination including a dilated fundoscopy or were too sick to be examined were excluded from the study. This study adheres with the tenants of the declaration of Helsinki.

Data on subjects demography, clinical history, time since diagnosis, chemotherapy received, history of diabetes and hypertension, hemoglobin, platelets, creatinine, and white blood cell count were collected. The examination of the eyes was done by an ophthalmologist at the bedside or in the eye department whenever possible. After history taking, visual acuity was recorded where possible using Snellen charts. Anterior segment examination was done using a flashlight and a Haag Streit slit-lamp (Haag Streit AG, Berne, Switzerland). Fundus examination was done by slit lamp biomicroscopy, binocular indirect ophthalmoscopy, after dilating pupils with 1% tropicamide eye drops. Fundus fluorescein angiography was done whenever possible.

The collected data were entered to and analyzed using the Statistical Package for Social Sciences for Windows software, version 16 (SPSS Inc., Chicago, Illinois, USA). An initial frequency count and percentages were obtained for all the data. Descriptive statistics were reported as means, frequencies, percentages, and proportions. Intergroup comparisons were performed using the Chi-square test. All $P < 0.05$ were accepted as statistically significant.

Results

Ninety-six subjects diagnosed with leukemia at the clinical hematology, hemato-oncology, and BMT unit of Christian Medical College and Hospital, Ludhiana, were examined for ocular changes during the study period. They comprised 61 (63.5%) males and 35 (36.5%) females, aged between 18 months and 91 years (mean = 39.73 ± 22.1). There were 79 adults and 17 children who were examined. The duration of the illness varied from 1 day to 5 years.

There were 53 newly detected and 43 follow-up leukemic in-patients. Of the total of 96 diagnosed cases of leukemia, 68 were acute and 28 chronic, 61 myeloid and 35 lymphoid. Their distribution by leukemia subtype was AML 43 (44.8%) subjects, ALL 25 (26%) subjects, chronic myelogenous leukemia (CML) 18 (18.8%) subjects, and chronic lymphocytic leukemia 10 (10.4%).

Ocular lesions were found in 42 (43.8%) subjects. Primary or direct leukemic infiltration was seen in 8 (8.3%) patients. Of the 8 patients with primary ophthalmic leukemia, 7 (87.5%) had AML and 1 (12.5%) had CML. All these were males [Figs. 1 and 2]. Secondary or indirect involvement

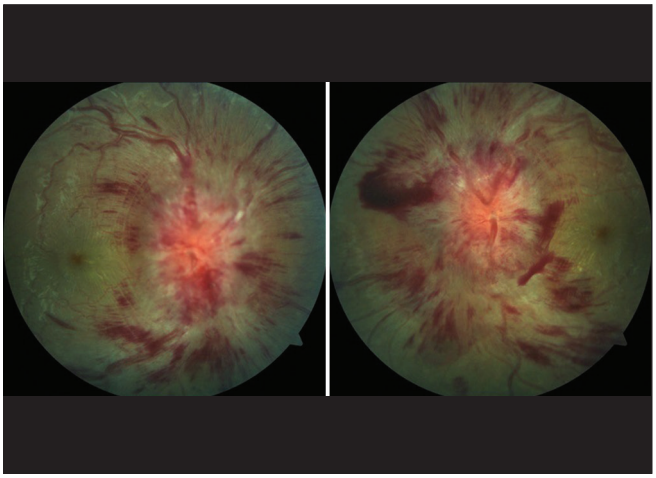

Figure 1: Primary leukemic infiltration in both eyes in acute myelogenous leukemia

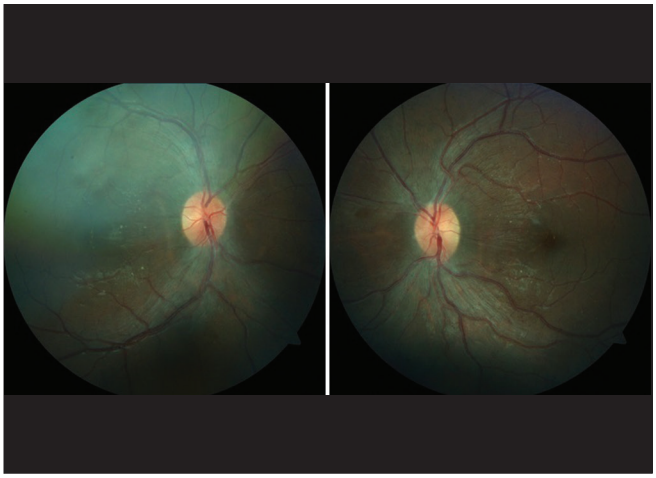

Figure 2: Resolution of primary leukemic infiltration after chemotherapy

due to anemia, thrombocytopenia, hyperviscosity, and immunosuppression were seen in 42 (43.8%) patients. Of the adult (n = 79) leukemic patients, 37 (46.8%) had leukemia related ocular changes while 5 (29.4%) of 17 children with leukemia had leukemic ophthalmopathy. Twenty-eight (45.9%) males and 14 (40%) females had evidence of ophthalmic leukemia [Fig. 3]. Thirty-five (51.9%) of the acute leukemias (n = 68) and 7 (25%) of chronic leukemias (n = 28) had leukemic ophthalmopathy [Fig. 4]. Thirty-two (52.9%) of the myeloid leukemias (n = 61) and 10 (28.6%) of lymphoid leukemias (n = 35) had ophthalmic manifestations of leukemia [Fig. 5].

The details of the number of patients with ocular findings in the different leukemias are given in Table 1.

Fifty-two (54.2%) subjects were undergoing chemotherapy while 44 (45.8%) subjects were not undergoing any form of treatment prior to ophthalmic evaluation. Of these subjects, 22/52 (42.3%) who had chemotherapy had changes while 20/442 (45.5%) of those who did not have chemotherapy had changes. Six of the study subjects had undergone BMT.

Primary or secondary ophthalmopathy due to leukemia were present in 22/53 (41.5%) new patients and 20/43 (46.5%) revisit patients. The remaining 54 (56.3%) subjects had no clinical evidence of ocular changes due to leukemia. Only 12 patients out of 96 (12.5%) had eye symptoms on presentation–proptosis–1, red eye–3, and decreased vision in 8. The prevalence of various ocular changes in the leukemia patients is shown in Table 2.

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. This is so because the eye symptoms may be the initial mode of presentation of the systemic illness, or the first manifestation of relapse after remission–inducing chemotherapy.[2]

Leukemia may present with or be associated with ocular disorders. The prevalence of ocular involvement in leukemic patients has been reported to be between 9% and 90% in various studies.[2,11-15] This divergent variation in results may imply the transient nature of leukemic ocular findings, which may wax and wane with time and treatment. It may also be due to the varied study designs being used. It is estimated that up to 69% of all patients with leukemia show fundus changes at some point in the course of their disease.[11] Prior to the era of the modern chemotherapy, massive leukemic infiltrates were often seen accompanying hemorrhages, partially or completely destroying retinal architecture.[2] Leonardy *et al*.[3] in an analysis of 135 autopsy eyes for ocular involvement found that although leukemic infiltrates in many patients were extensive, they were not detected clinically, perhaps because detailed ophthalmological examinations were rarely performed on terminal cases of leukemia with no severe visual impairment. In this study, primary or direct leukemic infiltration was seen in 8.3% patients while secondary or indirect involvement was seen in 43.8% of patients. Although 54.2% of patients were on chemotherapy, only one patient had a grade 2 conjunctival graft versus host disease, and one patient had a dry eye at the time of examination.

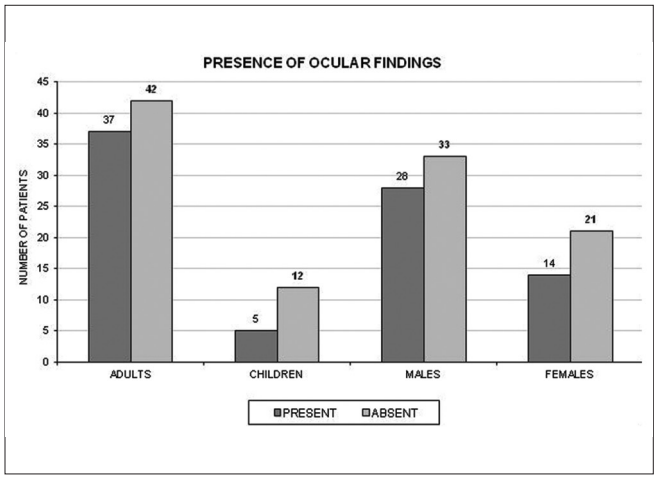

Figure 3: Demographic profile of the presence of ocular findings

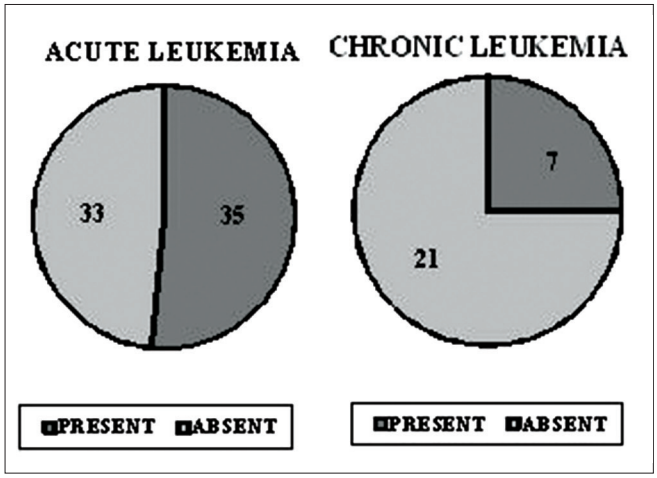

Figure 4: Presence of ocular findings in acute and chronic leukemias

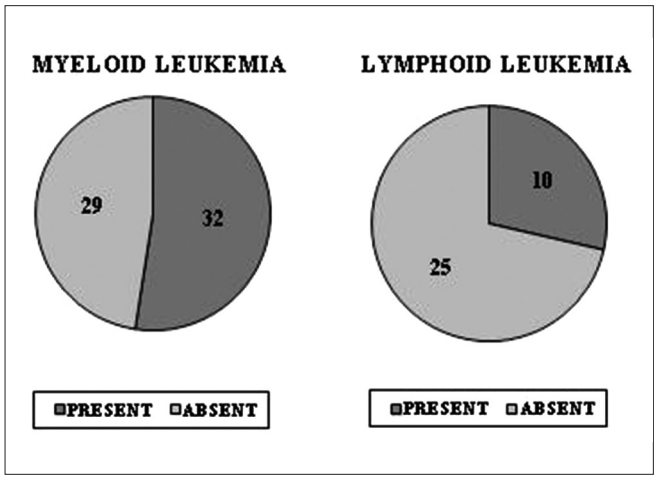

Figure 5: Presence of ocular findings in myeloid and lymphoid leukemias

The 43.8% prevalence of leukemic ophthalmopathy documented in this study is comparable to 35.4% reported in Malaysia[12] and 39% in America,[16] but differed from

69% reported in Ethiopia[11] and 77.8% in Nigeria.[17] This could be due to inherently higher prevalence of leukemic ophthalmopathy among Africans, or the consequences of deficient human and material resources needed for timely and effective management of systemic leukemia in Africa.[2,11,17,18]

Orbital and ocular lesions have been reported to be the third most frequent extramedullary location of acute leukemias after the meninges and testicles.[14] It is important to take a closer look at sites of extramedullary leukemic infiltration both because of their local morbidity and because these sites may act as a reservoir for proliferation of leukemic cells, which may eventually result in systemic relapse.[19] Furthermore, improved survival of patients with leukemia has led to an increase in variability of ocular presentations. This may also be due to the side effects of the treatment.[5]

This study cohort did show a preponderance of males; 61 males (63.5%) out of a total of 96 subjects. This trend is similar to reports from Ethiopia[11] to Malaysia.[12] The observed sex distribution as reported earlier could be due to natural sex prevalence pattern of leukemia or the established pro-male gender inequity in access to healthcare[20] or both. This seems to suggest the need to identify and overcome gender-related healthcare access barriers and has important implications for healthcare planners and implementers.[17] Twenty-eight males had ocular changes (28/61) 45.9% whereas 14/35 (40%) of females showed ocular changes due to leukemia; however, there were no statistically significant gender-based differences in the presence of leukemic ophthalmopathy.

Table 1: Ocular findings in the different leukemias

Condition	Number of patients with ocular findings	Total number of patients	Percentage with ocular findings
AML	27	43	62.8
ALL	8	25	32
CML	5	18	27.9
CLL	2	10	20

AML: Acute myelogenous leukemia, ALL: Acute lymphocytic leukemia, CML: Chronic myelogenous leukemia, CLL: Chronic lymphocytic leukemia

The varied findings of the leukemias in the eye are described in Table 2. This varies across different studies due to the transient nature of the disease or its complications. The posterior segment complications result predominantly from secondary hematological complications caused either by the systemic leukemia or its treatment rather than primary leukemic ocular infiltration [Fig. 6].[2,16]

There were 79 adults and 17 children who were examined. Among the adults, 37/79 (46.8%) had ocular changes while 5/17 (29.4%) of children had changes. Reddy *et al*.[12] in a study of 288 cases of leukemia found that 49.1% of adults had ocular involvement as compared to only 16.5% of children. Guyer *et al*.[21] studied retinal changes in acute leukemias only and found 73.9% of adults had changes versus only 15.9% of children.

Myeloid leukemias were more commonly observed to have ocular manifestations, 32/61 (52.9%) as compared to lymphoid leukemias, 10/35 (28.6%). This was similar to the findings of the other major studies.[12,16,17,21] Acute leukemia patients in this study had significantly more ocular manifestations than chronic patients (51.9% vs. 25%) Fisher exact *t*-test, P – 0.01467. This was similar to the findings of Reddy *et al*.,[12] Omoti *et al*.,[22] Kincaid and Green,[2] and Leonardy *et al*.[3] However, studies by Eze *et al*.[17] and Nelson *et al*.[23] found chronic leukemias to have more ocular findings than acute ones. This discrepancy could be either because of different study designs or may be an actual reflection of the disease. Subjects with AML had the highest incidence of ocular manifestations (62.8%). This was similar to studies by Reddy *et al*.[12] and Omoti *et al*.[22] These details are given in Table 3. In the acute group, there was a significant difference (Chi-square 2.85, P = 0.045) between adults 29/48 (60.4%) and 6/20 (30%) children with respect to ocular manifestations; adults had a significant association with ocular manifestations.

Table 2: Ocular changes in leukemia (*n*=96)

Primary/direct changes	*n* (%)	Secondary/indirect changes	*n* (%)
Infiltration of ocular tissues		Retinal changes	
Granulocytic sarcoma with proptosis due to orbital infiltration	1 (1)	Superficial hemorrhages	29 (30.3)
Optic nerve infiltration	3 (3.1)	Deep intraretinal hemorrhages	22 (23.2)
Choroidal infiltration (exudative retinal detachment)	2 (2.1)	White centered hemorrhages	6 (6.3)
Neuro-ophthalmic changes		Dilated/tortuous veins	8 (8.4)
Papilledema	5 (5.2)	Cotton wool spots	7 (7.3)
Retinal changes		Subhyaloid hemorrhages	10 (10.4)
White centered hemorrhages with leukemic infiltrates	5 (5.2)	Vitreous hemorrhage	1 (1)
		Branch retinal vein occlusion	1 (1)
		Disc hemorrhages	1 (1)
		Other changes	
		Dry eye	3 (3.1)
		Subconjunctival hemorrhage	2 (2.1)
		Corneal ulcer	1 (1)
		Conjunctivitis	2 (2.1)
		Conjunctival GVHD*	1 (1)

*GVHD=Graft versus host disease (some of the patients had more than one ocular finding in one or both eyes. Hence, the total numbers of findings are more than the number of patients with ocular changes)

Table 3: Comparison of the various studies

	Current study, India	Reddy *et al*.,[12] 2003, Malaysia	Omoti *et al*.,[22] 2010, Nigeria	Eze *et al*.,[17] 2010, Nigeria
Patients evaluated	Acute and chronic Adults and children New and follow-ups	Acute and chronic Adults and children Only new patients	Acute and chronic Adults only Only new patients Those not on chemotherapy	Acute and chronic Adults New and follow-ups
Total number	96	288	47	72
Age	18 months to 91 years	6 weeks to 78 years	20-70 years	18-72 years
Ocular findings (%)	42/96 (43.8)	102/288 (35.4)	7/47 (14.9)	56/72 (77.8)*
Ocular manifestations in adults/children (%)	Adults=37/79 (46.8) Children=5/17 (29.4)	Adults=82/167 (49.1) Children=20/121 (16.5)	Adults=7/47 (14.9)	Adults=56/72 (77.8)*
Ocular manifestations in acute/chronic (%)	Acute=35/68 (51.9) Chronic=7/28 (25)	Acute=87/245 (35.5) Chronic=15/43 (34.9)	Acute=4/14 (28.6) Chronic=3/33 (9.1)	Acute=16/22 (72.7) Chronic=39/48 (81.3)
Ocular manifestations in myeloid/lymphoid (%)	Myeloid=32/61 (52.9) Lymphoid=10/35 (28.6)	Myeloid=62/151 (41) Lymphoid=40/137 (29.2)	Myeloid=6/23 (26.1) Lymphoid=1/24 (4.2)	Myeloid=27/37 (73) Lymphoid=28/33 (84.9)
Ocular manifestations in various diseases (%)	AML=27/43 (62.8) ALL=8/25 (32) CML=5/18 (27.8) CLL=2/10 (20)	AML=47/113 (41.6) ALL=40/132 (30.3) CML=15/38 (39.5) CLL=0/5 (0)	AML=4/9 (44.5) ALL=0/5 (0) CML=2/14 (14.3) CLL=1/19 (5.3)	AML=5/9 (55.6) ALL=11/13 (84.6) CML=22/28 (78.6) CLL=17/20 (85) BPL**=1/2 (50)
Ocular symptoms (%)	12/96 (12.5)	29/288 (10)	27/57 (57.4)*	38/72 (66.9)*

*Includes findings nonspecific to leukemia, **BPL: Bi-phenotypic leukemia, AML: Acute myelogenous leukemia, ALL: Acute lymphocytic leukemia, CML: Chronic myelogenous leukemia, CLL=Chronic lymphocytic leukemia

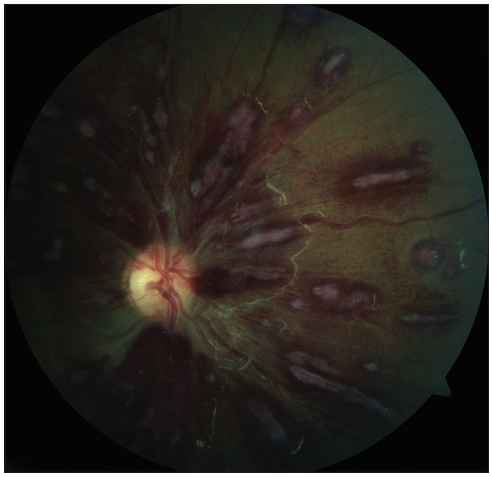

Figure 6: Anemic and thrombocytopenic retinopathy in acute myelogenous leukemia

The present study like many of the previous studies documented only clinically evident leukemia related ocular findings thus probably missing the occult manifestations. It is sometimes difficult for the physician to appreciate the ocular manifestations of leukemia because most subjects remain asymptomatic. This definitely has implications for ophthalmologists involved in the care of leukemic patients that mandatory and periodic eye check-ups at least every 6 months are a must despite the apparent noninvolvement of the eye.

There were a few limitations of this study. The number of subjects with chronic leukemias and children with leukemias are probably too small to draw definitive conclusions. Second, ultrasonography of the eye, computed tomography scan, or magnetic resonance imaging scan was not done routinely in all subjects to look for choroidal involvement of leukemia.

Conclusions

From the results of the present study, we conclude that secondary or indirect involvement of the retina is the most common eye change in leukemia. Ocular involvement is more often seen in acute leukemias and myeloid leukemias. Acute leukemias 35/68 (52.9%) had a significantly greater association with ocular manifestations as compared to chronic 7/28 (25%). In the acute group, there was a significant difference between adults and children with respect to ocular manifestations; adults had a significant association with ocular manifestations. All primary leukemic infiltrations were seen in males.

Although the ophthalmologist has a secondary role in the treatment of leukemias, a prompt recognition of the ocular manifestations is crucial because of the poorer prognosis associated with ocular involvement[7] and to identify possible extramedullary disease.[5] All leukemia patients should have an ophthalmic assessment at diagnosis and periodically at least every 6 months thereafter. Many have no symptoms despite ophthalmic involvement which could be an early sign of CNS disease or relapse.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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