Original Article

Ophthalmic manifestations of leukemias in Aminu Kano Teaching Hospital, Kano, Nigeria

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Abstract

Background: Haematological disorders, particularly leukemias, constitute a significant public health burden in Nigeria due to their associated morbidity and mortality. This study aimed to evaluate the ophthalmic manifestations of leukemia among patients at Aminu Kano Teaching Hospital (AKTH), Kano. **Methodology:** A cross-sectional study was conducted among 61 patients with confirmed leukemia attending AKTH. Data were collected using a semi-structured questionnaire and analysed with SPSS version 22. **Results:** Among the participants, 36 (59.0%) were males, with a mean age of 29.7 ± 13.1 years. Chronic myeloid leukemia was the most common subtype (52.5%), followed by chronic lymphocytic leukemia (23.0%), acute myeloid leukemia (16.4%), and acute lymphoblastic leukemia (8.2%). Ocular manifestations attributable to leukemia were observed in 21.3% of patients, with retinal venous tortuosity being the most frequent finding (13.1%). Other manifestations included lid changes (8.2%), conjunctival changes (3.3%), and proptosis (1.6%). Ocular involvement was highest among patients aged 6–15 years (8.2%) and lowest among those aged 16–25 and 26–35 years (1.6% each). A statistically significant association was found between ocular changes and low-level occupation (p = 0.03). Ocular manifestations were more common in patients with high white blood cell counts (9.9%), low red blood cell counts (16.4%), and low platelet counts, with the latter showing a statistically significant association. **Conclusion:** Ocular involvement is relatively common in leukemia and may have prognostic significance. Routine ophthalmic screening at diagnosis and during follow-up is recommended, particularly for patients with identified risk factors.

Keywords: Ophthalmic, manifestations, leukemia, patients, Kano, Nigeria

Introduction

Haematological disorders affect millions of people world over and it is of rising concern in Nigeria, representing a major public health problem due to its potential for significant morbidity and mortality.[1] Leukemia is a malignant proliferative disorder of haemopoietic bone marrow stem cells associated with over-crowding of the bone marrow by neoplastic leucocytes and widespread infiltration of organs, tissues, and peripheral blood by immature leucocytes.[1-4] They are classified into myeloid or lymphoid based on their origin and into acute and chronic depending on the clinical course. The chronic leukemias arise from the lymphoid (chronic lymphocytic leukemia, CLL) or myeloid (chronic myelocytic leukemia, CML) precursor cells.[4] They are different from acute leukemias in that the morphology of the cell lines show marked differentiation. On the other hand, acute leukemias are divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

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Understanding the burden and pattern of the ocular manifestations of leukemia is important not only because of the frequency with which eye changes are seen, but because the eye often reflect the disease state of the body.[1] Eye changes may be the initial mode of presentation, the first manifestation of relapse of the systemic illness, or the effect of the therapeutic agents used in treating the disease. In addition, patients with hematopoietic neoplasms are often immunosuppressed, so they tend to develop opportunistic ocular infections.[2] Orbital and ocular lesions have also been reported to be the third most frequent extramedullary location of acute leukemias after the meninges and testicles.[3] Leukemias may present with or be associated with ocular features. Ocular disorders have been reported in 30-90% of cases of leukemia.[1,3,5–7] Many patients with chronic leukemias are asymptomatic while other patients present with splenomegaly, fever, weight loss, malaise, frequent infections, bleeding, thrombosis, or lymphadenopathy.[8,9-13] Furthermore, improved survival of patients with leukemia has led to an increase in variability of ocular presentations in the form of side effects of the treatment and the ways leukemic relapses are being first identified as an ocular presentation.

Of all leukemia patients, about 5% have been reported to develop visual loss attributable to the underlying condition.[14] Leukemic ophthalmopathy, symptomatic or asymptomatic, may result from direct ocular infiltration by leukemic cells, indirect ocular involvement resulting from secondary hematologic changes, opportunistic infections and complications of various modalities of therapy i.e. cytotoxic drugs, total body irradiation, and allogenic bone marrow transplantation.[8,15–18] The direct leukemic infiltration can show three patterns: anterior segment uveal infiltration, orbital infiltration, and neuro-ophthalmic signs of central nervous system 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, hyper-viscosity, and immunosuppression.[8] These can manifest as retinal or vitreous hemorrhage, infections, and as vascular occlusions. In some cases the ocular involvement may be asymptomatic.[1]

In the era before effective anti-leukemic therapy, retinopathy was believed to be of no prognostic significance in acute leukaemia.[19,20] However, recent reports have demonstrated that the presence of ocular involvement is associated with poor prognosis in acute childhood leukemias.[20] Therefore, it is important to consider an ophthalmic evaluation at the time of diagnosis of acute leukemia in both adults and children.[8] Understanding 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.[21]

Aminu Kano Teaching Hospital is a tertiary centre and the major tertiary health institution offering histo/cytopathology and specialized haemato-oncology services to Kano and the neighbouring states of Jigawa, Katsina, Bauchi, etc. Hence a significant number of patients with haematological malignancies are attended to.[22] To the best of our knowledge there is no data available on the ophthalmic manifestation of leukemia in this environment. In some patients, ocular symptoms and careful examination lead to a diagnosis of leukemia. However, some other times, cases of haematological malignancies are erroneously managed as primary ophthalmic cases, hence such patients are often referred to haemato-oncology clinics rather late.

Establishing common presenting features of leukemia will greatly facilitate early identification, leading to prompt referral and treatment. A high proportion of leukemia patients now achieve initial bone marrow remission with combination chemotherapy, it is therefore important to take a closer look at sites of extramedullary leukemic infiltration, because of their local morbidity and also because these sites may act as a reservoir for proliferation of leukemic cells which may eventually result in systemic relapse.[23] Furthermore, improved survival of patients with leukemia has led to an increase in variability of ocular presentations in the form of side effects of the treatment. Besides, leukemic relapses may be first identified as an ocular presentation.[8] Therefore, the determination of commonest ophthalmic manifestations of leukemia and the factors associated with them may not only ensure early diagnosis of leukemia, but also understanding the nature and extent of ocular complications can be assessed to determine if routine

screening for ocular disease can be justified in patients with haematological malignancies.

Methods

Study area

Kano State is situated in the North-Western geopolitical zone of Nigeria and has forty-four (44) Local Governments Areas (LGAs), with a population of over 15 million people.[24] The state has a land mass of 20760 square kilometers, with the following geographical coordinates: 120 37' North, 90 29' East, 90 33' South and 70 43' West. Aminu Kano Teaching Hospital was established in August 1988 although the decision to establish a teaching hospital in Kano was taken at the 15th meeting of the National Council on Health. The hospital is located on Zaria Road in Tarauni Local Government Area of Kano State and belongs to the government of the Federal Republic of Nigeria under the supervision of the Federal Ministry of Health. It was designed as a 500 bedded teaching hospital but currently has over 700 bed capacity.[24]

The Haematology clinic is located within the hospital and is run by Consultants and Residents Doctors with an average number of 80-90 patients per week out of which an average of 5-7 patients have leukemia. Recruitment involved patients coming for routine follow up for leukemias. The eye clinic is also located within the hospital and is a few meters from hematology clinic.

Study design

This was a hospital-based cross-sectional study among patients with leukemia.

Study population

Leukemia patients attending the Haematology clinic, and those admitted to the Paediatric Haematology Ward and Medical Wards were included in the study. This included both newly diagnosed and follow up cases. We excluded patients who were too ill to have detailed eye examination and those with recent history of intraocular surgery. The study was conducted over a period of one year.

Sample size determination

Sample size for the study was estimated using the formula for single proportion ($n = Z^2pq/d^2$).[25] Using the value of standard normal deviate corresponding to 95% confidence interval; proportion of leukaemia patients with ocular disease (15%) obtained from a previous study[26] and desired level of precision of 95% [$n = (1.96)^2x0.15x0.85/(0.05)^2 = 49$]. Adding a non-response of 10% to the calculated sample size, a minimum sample size of 54 was obtained.

Sampling technique

All eligible patients comprising newly diagnosed and those reporting for follow up with leukemia at hematology clinic and those admitted at the medical wards were examined for ophthalmic manifestation till the sample size was obtained.

We included all patients diagnosed with leukemia from bone marrow aspiration biopsy in Aminu Kano Teaching Hospital and excluded leukemia patients with previous diagnosis of eye diseases like glaucoma, cataract, or other retinal diseases.

Data collection and management

The instrument for data collection was a structured questionnaire adapted from a study consisting of 3 sections namely, socio-demographic characteristics of respondents, visual status and pattern of ophthalmic manifestations.[27] This was then used in documenting demographic data, type of leukemia, duration of illness, and modality of treatment from their Hematology/Immunology clinical charts.

Leukemia was diagnosed using clinical data and cytological analysis of peripheral blood smears and bone marrow samples.[26] Patient eye examinations followed ethical guidelines (Helsinki Declaration).[28] Visual acuity was measured with Snellen and Illiterate "E" charts, and pinhole testing was used to refine best corrected visual acuity (BCVA). Visual impairment was defined as BCVA worse than 6/18.[26]

Proptosis was assessed clinically with a Hertels exophthalmometer, and pupillary reflex was checked with a pen torch. The anterior eye segment was examined using a Carl Zeiss slit lamp to identify abnormalities such as conjunctival venous changes, corneal issues, hypopyon, iris atrophy, lens opacity, and anterior chamber details. Intraocular pressure was measured via Goldmann applanation

tonometry.[29] For the posterior segment, pupils were dilated, and the fundus was examined with specialized lenses and microscopes to detect vitreous haemorrhages, retinal abnormalities (haemorrhages, exudates, detachment), and optic disc pathology (swelling, haemorrhages, pallor).[29]

Pre-testing of the questionnaires was done by administering 10% of the sample size. This was conducted at Murtala Muhammad Specialist Hospital which is in a different local government (Kano Municipal) from Aminu Kano Teaching Hospital located in Tarauni LGA. This was aimed at assessing the clarity of the questions, assessing internal consistency of the questionnaire and average duration of administering each questionnaire.

Ophthalmic Nurse and one Optometrist volunteered as research assistants. The ophthalmic nurse and optometrist were trained on how to fill out the relevant sections of the questionnaire and helped out in carrying out visual acuity assessment and refraction. The detailed activity plan is shown in **Figure 1.**

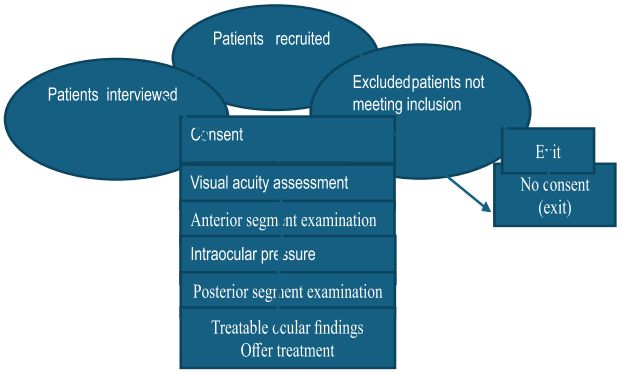

Figure 1: Activity flow chart

Data Analysis

The collected data was coded and entered into two separate excel sheets and compared for consistency. It was then analyzed using the Statistical Package for Social Sciences for Windows software, version 22 (SPSS Inc., Chicago, Illinois, USA). Qualitative variables (gender, ocular findings, type of leukemia, etc) were summarized using frequencies and percentages and compared using Chi square test. While quantitative variables (age, hematological parameters like PCV, WBC, etc) were summarized as means and standard deviations and compared using t-test. Factors found to be significant at bivariate level were entered into a logistic regression model to adjust for possible confounding. All $p \leq 0.05$ was accepted as statistically significant.

Ethical considerations

The study adhered to the tenets of Helsinki Declaration.[28] The Health Research Ethics Committee of AKTH gave approval (NHREC/21/08/2008/AKTH/EC/1778) for the study which was carried out at both the Departments of Ophthalmology and Hematology, AKTH, Kano. After explaining the aim of the study as well as the details of the examination to be carried out, informed consent from adult patients, and assent form for minors (age < 18years) were obtained from patients/parents/caregivers who agreed to participate in the study. All information collected on the patients was considered confidential and treated as such. Patients with treatable ocular manifestations were offered appropriate treatment at no cost to the patients.

Results

One hundred and twenty-two eyes (122) eyes of 61 patients were examined. The age range was 6 to 52 years with a mean age of 29.7 ± 13.1 years. There were 36(59.0%) males and 25(41.0%) females (M: F = 1.4:1). Of the 61 patients examined, 13(21.3%) were newly diagnosed while 48(78.6%) had been on follow up for over one month and all the patients had commenced chemotherapy at the time of the study (Table 1).

Variables	Frequency (n=61)	Percentage (%)
Age group		
6 - 15 years	13	21.3
16 - 25 years	7	11.5
26 - 35 years	18	29.5
36 - 45 years	17	27.9
> 45 years	6	9.8
Gender		
Male	36	59
Female	25	41
Tribe		
Yoruba	5	8.2
Igbo	2	3.3
Hausa/Fulani	52	85.2
Others	2	3.3
Occupation		
Senior Public Servant	2	3.3
Intermediate Grade Public Servant	4	6.6
Junior Skilled Worker	1	1.6
Semi-Skilled Worker	5	8.2
Unemployed.	49	80.3
Literacy level		
None	28	45.9
Primary	13	21.3
Secondary	9	14.8
Tertiary	11	18

The commonest type of leukemia was CML (52.5%) and ALL (23%). All the 61 recruited patients had commenced treatment with AML patients receiving cyclophosphamide and vincristine; doxorubicin and cytosine arabinoside for AML patients, chlorambucil and vincristine for CLL patients while CML were receiving Hydroxyurea and imatinib and up to 28(45.9%) had been admitted previously (Table 2). Further, only 11(18%) presented with a visual acuity of 6/9 or worse. Only one patient presented with visual acuity of light perception (Table 3).

Table 2: Distribution of leukemia by type and treatment regimen in AKTH

Variables	Frequency (n=61)	Percentage (%)
Leukaemia type		
Acute lymphoblastic (ALL)	5	8.2
Acute myeloid (AML)	10	16.4
Chronic Lymphocytic (CLL)	14	23
Chronic Myeloid (CML)	32	52.5
Treatment regimen		
Cyclophosphamide+ vincristine	5	8.2
Doxorubicin+ cytosine arabinoside	10	16.4
Chlorambucil+ vincristine	14	23
Hydroxyurea + Imatinib	32	52.5

Table 3: Visual acuity status of leukemia patients in AKTH

Visual Acuity	Right Eye	Left Eye
Presenting Visual Acuity		
6/6	49(80.3)	48 (78.7)
6/9	7(11.5)	9 (14.8)
6/12	2(3.3)	0(0)
6/18	1(1.6)	1(1.6)
6/24	1(1.6)	1(1.6)
6/36	0(0)	1(1.6)
6/60	0(0)	0(0)
Light Perception	1(1.6)	1(1.6)
Total	61(100)	61 (100)

Of the 61 patients assessed, only (1.6%) reported history of ocular symptoms of pain, redness, and foreign body sensation unrelated to their leukemia, others (8.2%) had previous eye diseases mostly identified to be allergic conjunctivitis (Figure 2). Table 4 showed the platelet count was found to show significant variation and was lower in patients that have had leukemia diagnosis for more than 6 months

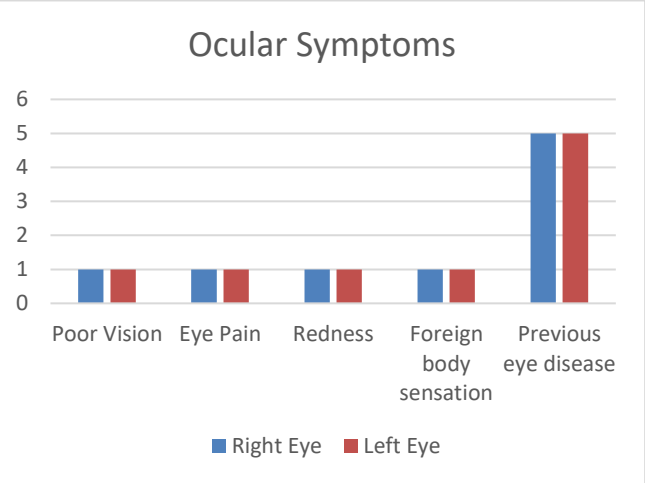

Figure 2: Ocular symptoms among leukemia patients in AKTH

Table 4: Haematological parameters in patients with leukemia taken from peripheral blood in AKTH

Parameters	n	Minimum	Maximum	Mean	Std. Deviation
White Blood Cells	61	2.1	87	9.86	10.7
Red Blood Cells	61	1.2	6.2	4.12	0.9
Platelets	61	66	850	265.34	128.9

Table 5 revealed leukemia related ocular changes among the patients was found to be (21.3%) and it was highest for retinal venous tortuosity (13.1%); the remaining were lid changes (8.2%), conjunctival changes (3.3%), and proptosis (1.6%). The association between type of leukemia and positive eye findings were not statistically significant (Table 6). However, there was statistically significant ($p = 0.03$) association between leukemia changes and low-level occupation (Table 7) and same was found for positive leukemia eye changes and low platelet count ($p=0.03$) (Table 8).

Table 5: Ophthalmic manifestations of leukemia patients in AKTH

Ocular manifestation	Frequency (%) n = 61
Proptosis	1 (1.6)
Restricted eye movement	1 (1.6)
Eye Lid changes	5 (8.2)
Conjunctival Changes	2 (3.3)
Corneal changes	1 (1.6)
Disc Changes	1 (1.6)
Retinal venous tortuosity	8 (13.1)
Intraretinal haemorrhages	1 (1.6)
Exudates	1 (1.6)

Table 6: Pattern of leukaemia related ocular features by leukemia type in AKTH

Leukemia type	Eye Findings		Total n (%)	p-value
	No n (%)	Yes n (%)		
Acute lymphoblastic Leukaemia	2 (3.3)	3 (4.9)	5 (8.2)	0.084
Acute Myeloid Leukaemia	7 (11.5)	3 (4.9)	10 (16.4)	
Chronic Lymphocytic Leukaemia	13 (21.3)	1 (1.6)	14 (23)	
Chronic Myeloid Leukaemia	26 (42.6)	6 (9.8)	32 (52.5)	

Table 7: Socio-demographic pattern of leukemia-related ocular features in AKTH

Socio-demographic variables	Leukemia changes		Total n (%)	p-value
	No n (%)	Yes n (%)		
Gender				
Male	27 (44.2)	9 (14.8)	36 (59.0)	0.399
Female	21 (34.4)	4 (6.6)	25 (41.0)	
Tribe				
Yoruba	4 (6.6)	1 (1.6)	5 (8.2)	1.00
Igbo	2 (3.3)	0 (0.0)	2 (3.3)	
Hausa	40 (65.6)	12 (19.7)	52 (85.3)	
Others	2 (3.3)	0 (0.0)	2 (3.3)	
Occupation				
Senior public servant	0(0.0)	2(3.3)	2(3.3)	0.028
Intermediate Grade Public Servant	4(6.6)	0(0.0)	4(6.6)	
Junior Skilled Worker	0(0.0)	1(1.6)	1(1.6)	
Semi-Skilled Worker	4(6.6)	1(1.6)	5(8.2)	
Unemployed	40(65.6)	9(14.8)	49(80.4)	

Table 8: Risk factors for ophthalmic manifestation of leukemia

Haematological parameters (peripheral blood sample)	Leukemia Changes		Total n (%)	P-value
	No n (%)	Yes n (%)		
White blood cell count				
Low White blood cell count	4 (6.6)	2 (3.3)	6 (9.9)	0.235
Normal White Blood Cell Count	30 (49.2)	5 (8.2)	35 (57.4)	
High White Blood Cell Count	14 (23.0)	6 (9.9)	20 (32.9)	
Red blood cell count				
Low red blood cell count	21 (34.4)	10 (16.4)	31 (50.8)	0.09
Normal red blood cell count	26(42.6)	3(4.9)	29 (47.5)	
High red blood cell count	1 (1.6)	0 (0.0)	1 (1.6)	
Platelet count				
Low platelet count	6 (9.8)	7 (11.5)	13 (21.3)	0.031
Normal platelet count	35 (57.4)	6 (9.8)	41 (67.2)	
High platelet count	7 (11.5)	0 (0.0)	7 (11.5)	

Discussion

The results of this study showed that ocular morbidity is common in patients with leukemia. Several of these ophthalmic features are potentially blinding conditions which may be related or unrelated to the disease and involvement of the retina is the most common eye change in leukemia observed in our study. In keeping with the previously reported prevalence pattern of leukemia,[26] more cases of chronic than acute leukemia were seen in our study. This was similar to what was found by other Nigerian studies[26,29] and different from those found in studies done in Malaysia and India.[30,31] This difference can be attributed to the fact that the incidence of chronic leukemia in Asia is lower than that of Africa.[1] Additionally, acute leukemia often run a rapid and fatal course compared with chronic leukemia and is further aggravated in the resource-constrained African setting by frequent delayed presentation with attendant adverse implications for prognosis and early mortality.

All the patients were on treatment with combinations of cyclophosphamide, vincristine, doxorubicin, cytosine arabinoside, chlorambucil, hydroxyurea and imatinib. Hence there was no difference in

treatment modality with other cases of leukemia.[32] Majority of the patients presented with good visual acuity. This was similar to what Schachat and colleagues reported,[14] but differs from what was observed by Eze and colleagues.[33] This can be explained by differences in the study cohorts, as Eze studied only adults. This focus may result in examining more chronic cases, thereby increasing the incidence of vision-threatening changes observed in chronic leukemias.[8] Other non-leukemia related symptoms of itching, foreign body sensation, eye pain were seen in only one patient. These are conditions which are common in the general population and not related to leukemia or its treatment. In a similar study in Ethiopia, a variety of miscellaneous ocular findings, such as cataract, pterygium, and pingeculum, were detected in one-third of all leukemia patients.[6] However, the presence of these findings indicates the importance and need for a complete ophthalmologic evaluation in the diagnosis, management and follow-up of leukemia patients. Most of the hematological parameters were found to be within normal range across all the leukemia types except for low red blood cell and low platelet counts. This can be due to all the patients having commenced chemotherapy with a sizeable number already in remission.

The conditions that were found to be directly related to the leukemia included proptosis, restricted ocular motility, eyelid edema, retinopathy, subconjunctival hemorrhage, disc swelling, retinal venous anomalies, intra-retinal hemorrhages, and exudates. This study showed the number of patients who had ocular involvement due to leukemia was less than the 30-90% reported in other studies.[5,6,16,34] The results was similar to that found by Omoti and colleagues in Nigeria.[26] This could be due to inherently higher prevalence of leukemic ophthalmopathy among black Africans or the consequence of deficient human and material resources needed for timely and effective management of systemic leukemia in Nigeria and Africa.[2] Further, some of the studies that reported a very high incidence may have included disorders which may not necessarily be related to leukemia.

The most common specific ocular manifestation of leukemia in this study was retinopathy and this is in keeping with reports from studies conducted in USA and in India.[8,35] There was only one patient with proptosis, similar to what Esmaeli *et al* found,[36] but different from what was obtained by Omoti in Nigeria, who found proptosis to be the most common specific ocular manifestation of leukemia.[26] This can be due to the fact that patients that have started chemotherapy were excluded in the Nigerian study. Similar to previous studies,[1,6,14] this study documented only the clinically evident leukemia related ocular lesions thus probably under-estimating occult manifestations like choroidal infiltration. Leukemia related ophthalmic changes were found to be highest among patients with CML and lowest in patients with CLL. This was similar to the findings of other studies in Nigeria, Malaysia and India.[30,31,33] The ocular involvement is likely due to direct leukemic infiltration, secondary hematologic abnormalities, treatment complications, or even pre-existing unrelated ocular pathology.

There was no statistically significant association between type of leukemia and positive eye findings, however chronic leukemias were found to have more ophthalmic features than acute leukemias. This differed from findings of a retrospective review by Kincaid & Green[2] and another study in USA,[35] but was similar to the findings by Eze and colleagues in Nigeria.[33] This discrepancy could be because of the difference in study designs. For example, the extensive series of Kincaid and Green included cases from as early as 1923, before the days of modern chemotherapy, which destroys leukemic infiltrates in tissues as well as circulating leukemic cells. Additionally, the patient in our study involved patients who had commenced chemotherapy, and this can account for the lower frequency of leukemia related ocular changes in this study. There was a statistically significant association between leukemia related eye changes and unemployment. This is likely because a significant number of the patients were unemployed or because unemployment negatively impacted on health care seeking behaviour, early diagnosis and prompt institution of management hence may increase the appearance of ocular features.

Risk factors for leukemia related ocular changes ranged from duration of leukemia, commencement of chemotherapy as well as differences in hematological parameters. There was a statistically

significant association between presence of leukemia related eye changes and low platelet count. It was also observed that there is a statistically significant association between low red blood cell count and presence of eye findings. Although this was found to be different from what was reported in autopsy series conducted in USA, where they found a similar correlation between leukocyte count and the presence of ocular leukemic cell infiltration.[35] Same study found Leukemic infiltrations of the eye to be associated with advanced systemic disease. These positive correlations suggest that ocular manifestations in leukemic patients may indicate advanced disease. These findings however cannot be used to establish hematological parameters as predictors of ophthalmic manifestations of leukemia because over the course of treatment there will be changes in the parameters. The results can also not rule out reverse causality because it is difficult to predict whether changes in hematologic parameters precede the disease, is a consequence of the disease or a side effect of chemotherapy until more extensive and cohort studies are carried out.

This hospital-based cross-sectional study may not accurately reflect conditions at the community level, and the use of convenience sampling to select participants could have introduced a higher risk of bias. Therefore, more comprehensive and methodologically robust studies, including longitudinal designs to monitor changes over time, are needed. Additionally, the use of ocular imaging techniques (such as OCT and fluorescein angiography) should be integrated to identify subclinical involvement and to better evaluate the risk factors associated with the ophthalmic manifestations of leukemia.

Conclusion: Given the potential prognostic implications of ocular involvement in leukemia, routine ophthalmic screening at diagnosis and during follow-up should be integrated into the multidisciplinary management of leukemia patients, especially among those with identified risk factors.

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