# Ophthalmic manifestations of leukemia and their association with hematologic parameters among adult patients in Jos, Nigeria

Ruth J Alfin,[1] Alice V, Ramyil,[2] Obadiah D Damulak,[3] Caleb D Mpyet[2]

**Abstract**

**Objective:** To determine the prevalence and pattern of ophthalmopathy in patients with leukemia, and their relationship with hematological parameters.

**Patients and Methods:** A cross sectional study of consecutive adult patients diagnosed with any leukemia, confirmed by bone marrow biopsy in two referral hospitals in Jos. Data was collected between January 2016 and June 2017. Socio-demographic and medical history were obtained from patients who consented to participate in the study. Results of the most recent hematologic parameters were retrieved from patient's case notes. Comprehensive ocular examination, including dilated fundoscopy was conducted and findings noted. Data was analysed using Statistical Package for Social Sciences version 21.

**Results:** Sixty-nine patients were examined during the study period. Their mean age was 44±18.8 years with a male to female ratio of 1.9:1. Forty-four (63.8%) participants had ocular manifestations. Leukemia specific manifestations were largely in the posterior segment (50.8%) and include tortuous retinal vessels (11.9%), retinal hemorrhage (10.2%), maculopathy (8.5%), disc swelling (5.9%) and cotton wool spots (5.1%). Non-leukemia specific manifestations such as cataract, pseudophakia and glaucoma accounted for 33.3% of findings. Significant predictors for occurrence of ocular manifestations were hemoglobin concentration (P=0.042) and platelet count (P=0.006). Increasing hemoglobin concentration may reduce the likelihood of developing retinal hemorrhage in 43.5% of cases (p= 0.007).

**Conclusions:** Ocular manifestations of leukemia were predominantly in the posterior segment and frequently associated with anaemia and thrombocytopenia.

**Key-words:** Leukemia, ophthalmic-manifestations, haematological-parameters, Jos

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## Introduction

Leukemia is a malignant clonal disorder of bone marrow stem cells that are responsible for producing white blood cells. It is considered a potentially blinding condition due to ocular complications that may be associated with it.

Leukemia comprises a group of malignancies arising from circulating white blood cells characterized by peripheral leucocytosis. The circulating leucocytes are either immature and or dysfunctional. Abnormalities may affect either the lymphopoietic or myelopoietic arms of hematopoiesis, resulting in lymphoid and myeloid leukemia respectively.[2,3] Leukemia can thus be classified into myeloid or lymphoid, acute or chronic based on the origin of the precursor cell and clinical course respectively.[1-3] This categorization accounts for the four broad classes of leukemia; acute myeloblastic leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL).

Ocular involvement in leukemia has long been documented and can affect nearly all ocular tissue with several published reports from developed countries but only a few from Subsaharan-Africa.[4-10] Ocular disorders of leukemia, symptomatic or asymptomatic may result from direct ocular infiltration by leukemic cells or indirect ocular involvement resulting from secondary hematologic changes or as complications of various treatment modalities such as chemotherapy, total body irradiation, or bone marrow transplantation.[2,3]

Previously published data on leukemia from Jos suggests that, it is the most frequently observed hematologic malignancy, but local data on ocular involvement is limited.[11-14] This study presents data on the frequency and pattern of ocular manifestation in adult patients with leukemia in Jos Nigeria and their relationship with hematologic indices.

## Patients and Methods

A descriptive, hospital-based study of adult (≥ 18yrs) patients with Acute myeloblastic leukemia (AML), Acute lymphoblastic leukemia (ALL), Chronic myelogenous leukemia (CML) and Chronic lymphocytic leukemia (CLL) irrespective of treatment status, being managed at the hematology and blood transfusion units of two major referral tertiary hospitals in Jos, between January 2016 and June 2017 (18months) was conducted.

The diagnosis of leukemia was made by examination of peripheral blood and bone marrow studies. All eligible patients who consented, were

[1]Department of Surgery, College of Medicine and Allied Health Sciences Bingham University, Jos campus. Nigeria. [2]Department of Ophthalmology, Jos University Teaching hospital. Jos, Nigeria.[3]Department of Blood transfusion and Hematology, Jos University Teaching hospital. Jos, Nigeria

All correspondences to:
Ruth J Alfin
Email: ruth.alfin@yahoo.com

consecutively recruited into the study. Patients who were unwilling to have a complete eye examination including dilated ophthalmoscopy or moribund patients who were unable to have full ocular examination were excluded. Ethical approval was obtained from the Ethical review committees of the two hospitals. At all times, the tenets of the Declaration of Helsinki for research involving human patients were upheld.

Patients were interviewed to obtain socio-demographic data, medical and ophthalmic history. Results of hemoglobin concentration (Hb), Total leucocyte count (TLC) and platelet count (PLC) routinely conducted for all patients on admission and a day prior to clinic visit for follow up patients were retrieved from their case notes. Clinical examination included that of the ocular adnexa with pen torch, slit-lamp examination of the anterior segment as well as dilated fundoscopy. Intraocular pressure was measured with a Goldman Applanation Tonometer after instilling 2 drops of Tetracaine and pre-staining with 2% fluorescein strips. The tonometer head was sterilized with 3.75% sodium hypochlorite solution and cleaned with normal saline after every use. Mydriatic fundus photographs were taken for patients with significant fundal pathology using a Canon CR-2 digital retinal camera (Canon Inc., Medical Equipment Group, 30–2, Shimomaruko 3-chrome, Ohta-ku, Tokyo, Japan.

Ocular abnormalities were classified as follows[8]**:**

a. Primary ocular complication: Likely to result from leukemic infiltrate and include proptosis, iris heterochromia, retinal leukemic infiltrates, and Roth spots.
b. Secondary ocular complications: Likely to result from hematological alterations such as anaemia, thrombocytopenia, hyper-viscosity or immune deficiency and systemic therapy. These include retinal haemorrhages (RH), vascular abnormality, disc swelling, cotton wool spots, vitreous haemorrhage and exudative retinal detachment.
c. Miscellaneous ocular abnormalities- Eye diseases unlikely to be related to leukemia such as pterygium, cataract, pseudophakia and glaucoma.

**Data management**

Data collected was entered into Statistical Package for Social Sciences version 21 and analysed. Frequency distribution tables were generated for all data collected. Fisher's exact test was used to test association between some categorical variables. Each hematologic parameter was assessed separately in relation to occurrence of ocular manifestation in a simple logistic regression model. Multivariable logistic regression model was then used to assess the independent effect of hematologic parameters that showed significance in the simple regression model with specific ocular manifestations. The results are presented in the form of tables. A P Value of $< 0.05$ was regarded as statistically significant for each variable of interest.

**Results**

A total of 138 eyes of 69 adult patients were examined for ocular changes during the study period. There were more males with a male to female ratio of 1.9:1. The mean age in this study was 44±18.8 with a range of 18 – 83 years. There was no statistically significant difference in age-gender distribution of the study group (Fisher's Exact P=0.26) as shown on Table 1.

Majority of the patients had chronic and myeloid forms of leukemia; 75.4% (52/69) and 63.8% (44/69) respectively. Chronic myeloid leukemia (CML) was the most common type of leukemia 47.8% (33/69) while acute lymphoblastic leukemia (ALL) was the least common 8.7% (6/69) as seen on table 2. Forty-four (63.8%) of the patients had ocular manifestations. Most participants with eye changes had CML followed by those with CLL and the least being those with ALL. The occurrence of ocular manifestation by leukemia subtype was not found to be statistically significant (Fisher's Exact P=0.24) as shown on table 2.

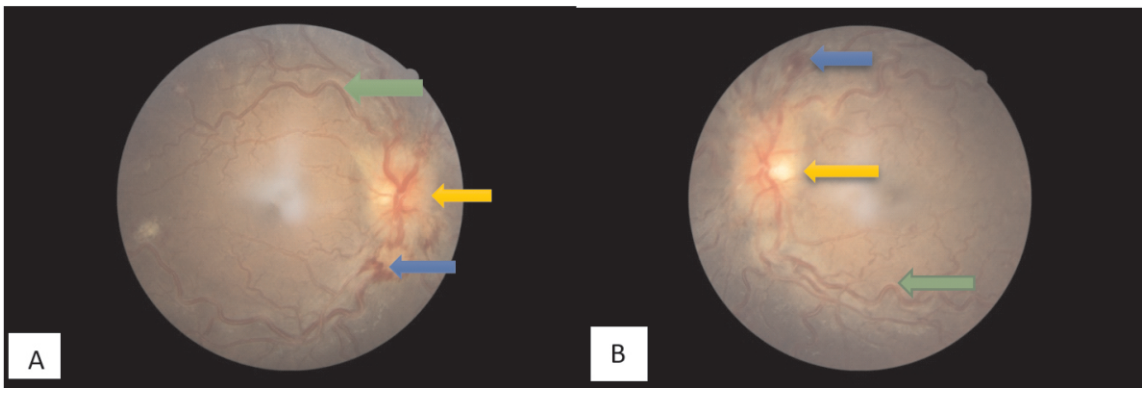


Figure 1: Fundal photograph A (Right eye) and B (Left eye) showing tortuous retinal vessels (green arrow), disc swelling (yellow arrow) and retinal hemorrhage (blue arrow) in a 28 years old female with CML

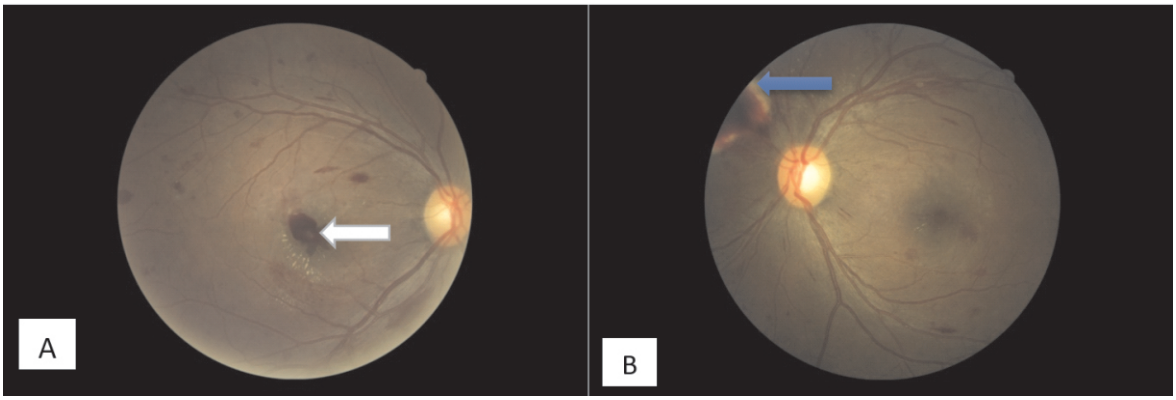


Figure 2: Fundal photograph A (Right eye) and B (Left eye) of a 33 years old male with AML, showing retinal (Blue arrow), macular hemorrhage and macular edema (White arrow).

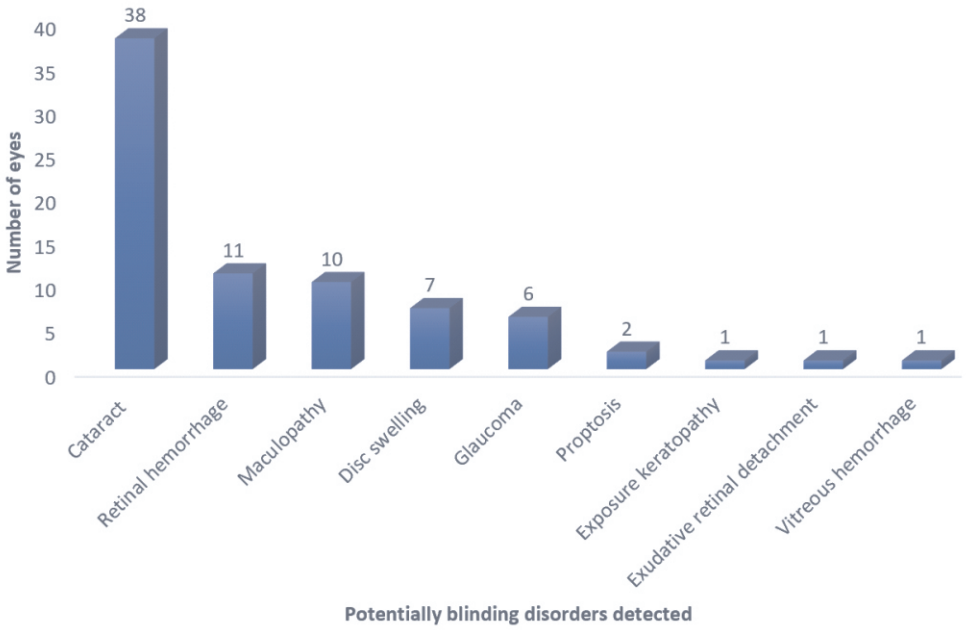


Figure 3: Potentially blinding disorders (by eyes) detected among adult leukemia patients in Jos

A total of 177 ocular manifestations were detected in eyes of 44 participants, 66.7 % (118/177) were leukemia specific while 33.3% (59/177) were miscellaneous. Of the disease specific disorders, the posterior segment had the most ocular findings 50.8% (60/118) followed closely by the ocular adnexa 46.6% (55/118) and the least being the anterior segment 2.5% (3/118). Tortuous retinal vessels 11.9% (14/118), retinal hemorrhage 9.3% (11/118), maculopathy 8.5% (10/118), disc swelling 5.9% (7/118) and cotton wool spots 5.1% (6/118) were the predominant findings of the posterior segment as illustrated in Figures 1 and 2. Cataract was the most frequent anterior segment pathology while pallor, conjunctival cock screw vessels and peri-orbital edema were the most common adnexa findings. One hundred (84.7%) of the leukemia specific ocular manifestations were due to secondary hematological alterations. Seventy-seven (43.5 %) of the all ocular changes detected were potentially blinding. They ranged from proptosis in the orbit to cataract and exposure keratopathy in the anterior segment. Posterior segment blinding conditions noted were glaucoma, disc swelling, RH, maculopathy, vitreous hemorrhage and exudative retinal detachment as illustrated in figure 3. Cataract, pseudophakia and glaucoma were non-leukemic findings observed among some participants (See table 3). The distribution of leukemia specific and non-specific ocular disorders by leukemia subtype was statistically insignificant.

The mean Hb of the study population was 9.11± 2.59g/dl. The distribution of PLC and TLC were skewed and so presented as median and interquartile ranges as shown on table 4. Simple logistic regression of presence of ocular manifestations with hematologic parameters revealed that Hb and PLC were the only hematologic

predictors for the occurrence of ocular manifestations among the study population. Increasing Hb decreases the odds of having ocular manifestation by 19.1% (P=0.04) and by 0.4% (P=0.006) for increasing PLC as depicted on table 5.

Table 1: Age-sex distribution of adult leukemia patients in Jos between January 2016 and June 2017

| Age group (years) | Sex | | |
|---|---|---|---|
| | Male N (%) | Female N (%) | Total N (%) |
| ≤ 20 | 3 (6.7) | 3 (12.5) | 6 (8.7) |
| 21-30 | 9 (20.0) | 8 (33.3) | 17 (24.6) |
| 31-40 | 10 (22.2) | 1 (4.2) | 11 (15.9) |
| 41-50 | 4 (8.9) | 1 (4.2) | 5 (7.2) |
| 51-60 | 9 (20.0) | 3 (12.5) | 12 (17.4) |
| 61-70 | 6 (13.3) | 7 (29.2) | 13 (18,8) |
| >70 | 4 (8.9) | 1 (4.2) | 5 (7.2) |
| Total | 45 (100) | 24 (100) | 69 (100) |

Table 2: Prevalence of ocular manifestation by leukemia type among patients in Jos between January 2016 and June 2017

| Type of Leukemia | Ocular manifestation present | | |
|---|---|---|---|
| | Present N (%) | Absent N (%) | Total N (%) |
| ALL | 4(9.1) | 2(8.0) | 6(8.7) |
| AML | 8(18.2) | 3(12.0) | 11(15.9) |
| CLL | 15(34.1) | 4(16.0) | 19(27.5) |
| CML | 17(38.6) | 16(64.0) | 33(47.8) |
| Total | 44(100.0) | 25(100.0) | 69(100.0) |

ALL- Acute lymphoblastic leukemia, AML-Acute myeloblastic leukemia, CLL-Chronic lymphocytic leukemia, CML- Chronic myeloid leukemia.

Fitting significant ocular manifestations into multiple logistic regression model shows that Hb is the only significant predictor of the presence of RH after controlling for PLC, type of leukemia and age of patient. With increasing Hb, the odds of RH occurring decreases by 43.5% (P=0.007) as shown on table 5.

**Discussion**

Knowledge of the ocular manifestations of leukemia is important because the eye has been reported as a frequent extra-medullary location for leukemic cells, and the only site where leukemic involvement of nerves and blood vessels can be directly observed.[8] Ocular involvement in leukemia may result from either direct infiltration of ocular tissues by leukemic cells (primary involvement) or secondary to hematologic alterations or ocular side effects of treatment.[4,] Leukemic ophthalmopathy may present prior to diagnosis of the systemic disease or may manifest during the course of treatment and follow up.[4,] Advances in diagnosis and treatment of leukemia have considerably improved the survival of patients, leading to an increase in the various ways leukemia can present in the eye.[5,8] Although all age groups can be affected, most cases of leukemia occur in adults.

The prevalence of ocular manifestations of 63.8% in our cohort is comparable to 69.2% reported by Jakkal[15] in India, 77.8% reported by Eze[10] and 70.0% documented by Ilo[16] in south-east and south-west Nigeria respectively. This differs moderately from reports of 43.8% and 52.2% by some authors from India[6,17] but contrasts markedly to 14.9% given by Omoti[9] in south-south Nigeria, 35.4% by Reddy[18] et al in Malaysia and 39.0% by Schachat[19] in United states of America. This divergent variation in prevalence of leukemic ophthalmopathy may be a reflection of the transient nature of ocular findings in leukemia which wax and wane with treatment.[8] The observed disparity may also be due to differences in case mix. Review of the above publications revealed that ocular manifestations were higher in studies that had more adults with chronic and myeloid leukemia's compared to those that had children in whom the leukemia is mainly acute, lymphoid and is more rapidly fatal.[6,10,15-19] Furthermore, although the role of therapy in the pathophysiology of some ocular changes in leukemia has been reported, it remains unclear if this wide variation in the frequency of ocular changes is related to the proportion of patients on therapy or their exclusion in some study designs.[8] A prospective research specifically designed to determine the effect of treatment on the course of ocular changes in leukemia would be appropriate before definitive conclusion can be drawn.

Chronic leukemia is the most common leukemia subtype among our study population. This is similar to previous reports from Nigeria[9,10,16] The high prevalence of ocular manifestations in CML compared with other subtypes in our cohort although not statistically significant is consistent with reports from other authors in Nigeria, Malaysia and India. [9,10,17-19,20] Possibly due to the low frequency of the acute leukemia's among adults while the rarer occurrence of ocular changes in CLL has been attributed to its indolent course when compared to CML.[18,21]

The pattern of ocular involvement in leukemia varies across different studies, probably due to the transient nature of the disease or its complications.[4,8,21] In our study, most of the leukemic ophthalmopathy detected were in the posterior segment and were largely from secondary causes. A similar distribution of posterior segment disorders has been described in some surveys.[10,16,22,] Potentially blinding conditions identified among our study subjects include vitreous hemorrhage, exudative retinal detachment, RH, disc swelling, maculopathy, glaucoma, proptosis and cataract. These

conditions are treatable but require early detection and, in some instances, prompt intervention to prevent blindness. Some ocular findings in our patients such as pterygium, cataract, pseudophakia and glaucoma were thought to be miscellaneous as their direct association with the disease have not been established. A variety of similar miscellaneous ocular findings were found among leukemia patients in Nigeria and the United States of America.[9,10,19] The detection of these miscellaneous disorders among our cohort highlights the importance of comprehensive ocular assessment of patients with leukemia.

Table 3: Pattern of ocular affectation in 44 leukemia patients with ophthalmopathy by anatomical location

| | Ocular adnexa/orbit | N | Anterior segment | N | Posterior segment | N | |
|---|---|---|---|---|---|---|---|
| Primary changes | *Proptosis | 2 | Iris heterochromia | 2 | *Disc swelling | 7 | |
| | - | - | - | - | Retinal infiltrate | 3 | |
| | - | - | - | - | Perivascular sheathing | 2 | |
| | - | - | - | - | Roth spots | 2 | |
| Secondary changes | Pallor | 32 | *Exposure- | 1 | Tortous retinal vessels | 15 | |
| | CCSV | 8 | keratopathy | | *Retinal hemorrhage | 11 | |
| | Periorbital oedema | 6 | | | *Maculopathy | 10 | |
| | Chemosis | 2 | | | Cotton wool spots | 6 | |
| | | | | | *Disc Hemorrhage | 2 | |
| | Conjunctiva injection | 2 | - | - | *Vitreous hemorrhage | 1 | |
| | Jaundice | 2 | - | - | Exudative retinal detachment | 1 | |
| | Subconjunctiva haemorrhage | 1 | - | - | | | |
| | | | - | - | - | - | |
| Miscellaneous changes | Pingueculum | 7 | *Cataract | 38 | *Glaucoma | 6 | |
| | Pterygium | 3 | Pseudophakia | 4 | Asteriod hyalosis | 1 | |
| Total | | 65 | | 45 | | 67 | 177 |

*NB: Some patients had two or more findings in two or more segments of one or both eyes. N- Frequency, CCSV-Conjunctival cock screw vessels, * potentially blinding*

Table 4: Hematologic profile of adult leukemia patients in Jos between January 2016 and June 2017

| Hematologic parameter | Mean N= 69 | Standard deviation | Minimum | Maximum |
|---|---|---|---|---|
| HB (g/dl) | 9.11 | 2.59 | 3.00 | 15.00 |
| PLC ($x10^9$/L) | 1500.00* | + | 20.00 | 1543.00 |
| TLC ($x\ 10^9$/L) | 460.00* | + | 1.00 | 1454.00 |

*HB- Hemoglobin concentration, PLC- Platelet Count, TLC- Total Leucocyte Count, *median, +not applicable*

In this study, presence of any ocular manifestation was significantly associated with anemia and thrombocytopenia. But Hb is the only significant predictor of the occurrence of RH. A similar association between RH, Roth spots and anemia was documented by Dhasmana[2] and his coworkers. Savyasonman[21] and colleagues in their study, reported that increasing Hb, reduced the likelihood of developing subhyaloid hemorrhage in patients with acute leukemia. On the contrary, Reddy[23] in his study of retinopathy amongst patients with acute leukaemia noted that there was no significant association between anemia with RH and Roth spots. Furthermore, some researchers from America and Malaysia reported that thrombocytopenia is significantly associated with leukemic retinopathy among patients with acute leukemia.[23] In this study, the odds for RH occurring reduced by 43.5% with increasing Hb. A similar study from India on the other hand, reported that the probability of developing subhyaloid hemorrhage decreased by more than 50% with increasing PLC.[21] There was no significant association between TLC of patients and the presence or absence of ocular manifestation in our study population. This tallies with findings from previous studies and corroborates the fact that although leukemia is primarily a white blood cell disorder, secondary hematological changes are responsible for most of the ocular changes.[21-24] Therefore, the presence of RH in the absence of any established

Table 5: Logistic regression identify factors predicting the occurrence of ocular manifestations and retinal hemorrhage among leukemia patients in Jos between January 2016 and June 2017

| Hematologic Parameter | Odds ratio (95% Confidence interval) | |
|---|---|---|
| | Ocular manifestation | Retinal hemorrhage |
| Hemoglobin concentration (g/dl) | 0.809 (0.659 - 0.993)** | 0.565 (0.374 - 0.853)** |
| Platelet count (x$10^9$/L) | 0.996 (0.994 - 0.9999)** | 0.999 (0.996 -1.002) |
| Total leucocyte count (x$10^9$/L) | 1.0033 (0.999 - 1.007) | + |
| CML | + | 1.000 |
| ALL | + | 1.027 (0.73 - 14.501) |
| AML | + | 1.325 (0.162 - 10.853) |
| CLL | + | 0.787 (0.085 - 7.310) |
| Age (years) | + | 0.992 (0.944 -1.042) |

*CML- Chronic Myeloid Leukemia, ALL- Acute Lymphocytic Leukemia, AML- acute Myeloid Leukemia, CLL- Chronic Myeloid Leukemia, *reference subgroup, ** P value <0.05, +variable not fitted into the model*

etiology in patients presenting to the ophthalmologist, should raise a high index of suspicion for leukemia, warranting a prompt hemato-oncologist evaluation and consultation.

**Conclusion**

Leukemic ophthalmopathy in adult patients is relatively common in our practice. Majority of the ocular changes are seen in the posterior segment of the eye. The predictors of the occurrence of ocular manifestations are Hb and PLC. Therefore, all adult leukemia patients, particularly those with anemia and thrombocytopenia should be referred early for ophthalmic evaluation to ensure early diagnosis and prompt treatment of any sight threatening condition.

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