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ORIGINAL ARTICLE

Images of Defaced Ocular Anatomy and Malignant Blood Disorders: An Evaluation of Inter-Relationship

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Abstract:

Objectives: To document spectrum of fundoscopic ocular findings and their association with malignant blood disorders in order to develop better diagnosis and treatment guidelines.

Methods: From March 2022 to February 2023, this study was conducted by joint effort of ophthalmology and hematology departments of Sheikh Zayed Hospital and RYK Hospital & Medical College. Participants with leukemia, lymphoma and multiple myeloma were included in study. Detailed eye examination and extensive hematological assessments were performed for every participant.

Results: The retrospective observational study included 90 cases of malignant blood disorders. In 86.66% cases, ophthalmic pathologies of sub-conjunctival hemorrhage, intra-retinal hemorrhage, cotton wool spots and retinal detachment were observed. Most dominant malignant blood disorder was acute lymphocytic leukemia having 35.55% cases, acute and chronic myeloid leukemia both had equal number of cases, 20.00% each. Anterior segment was involved in 12.22% of cases. Posterior segment was involved in 74.44% of the cases. Multivariable logistic regression analysis to assess the association between hematologic parameters and presence of ophthalmic findings revealed that total white cell count (TWCC) ($p = 0.031$) and total thrombocyte count (TTC) ($p = 0.046$) had statistically significant correlation with ocular pathologies.

Conclusion: The results suggest that retina is often directly or indirectly affected by malignant blood disorders, most common pathology being intra-retinal hemorrhage. In light of present study, it's evident to conduct an eye examination as a compulsory part of initial diagnosis for malignant hematologic conditions and to continue these checks regularly to identify any ophthalmic pathologies. *Al-Shifa Journal of Ophthalmology 2024; 20(4): 130-137.* *© Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan.*

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Introduction:

Pathologies of the erythrocyte, leukocyte, platelet, and illnesses of the coagulation and plasma proteins are all considered hematologic pathologies.[1] The terms leukemia, lymphoma and myeloma refer to malignant blood disorders which affect different cell types.[2] After almost thirty years, the hematologic malignancy that Thomas Hodgkin initially described in 1832 was dubbed Hodgkin disease in his honor.[3] Malignant hematopoietic diseases may reveal themselves as ocular symptoms due to direct invasion of ophthalmic tissues or indirect ophthalmic involvement linked to hematologic malignancies or therapeutic side effects.[4]The central nervous system (CNS) may be involved in intra-ophthalmic, adnexal, orbital tissue or

neuro-ophthalmic manifestations. Liebreich was the first to report leukemic retinopathy, the most clinically evident of all the ophthalmic symptoms in the 1860s.[5]Primary leukemic infiltrates can cause proptosis, optic nerve infiltration, cranial nerve palsy and choroidal infiltration. The majority of ophthalmic findings in lymphomas arise from direct infiltration of the orbit or intra-ophthalmic tissue. These pathologies appear as vasculitis, retinitis, uveitis, or conjunctival mass.[6]Through extra-medullary plasmacytoma or direct infiltration, multiple myeloma affects the orbital and ophthalmic tissue, resulting in symptoms such as proptosis, pressure exerting mass tumors, pathological corneal accumulations and cysts of ciliary body. Hyperviscosity syndrome of multiple myeloma, which is brought on by increased monoclonal immunoglobulins can cause retinopathy, retinal micro-aneurysm, infiltration of choroidal layer, and venous occlusion of retina is another pathogenic pathway of ophthalmic involvement.[7]Ophthalmic findings frequently correspond with the advancement of the disease, but they can also frequently be the earliest indication of an underlying malignant blood disorder and appear before systemic pathologies do.[8]Eye symptoms can also represent as single, focused recurrent appearing pathology following full recovery from systemic pathologies.[9] Therefore, a detailed ophthalmological evaluation is required for the diagnosis, recurrence, and prognosis of any patient diagnosed with malignant blood disorders.

Our research was concentrated on examining the range of ophthalmic findings linked with malignant blood disorders, as well as their relationship to different blood parameters. Malignant blood disorders often have systemic manifestations, and ocular signs can be an early indicator of underlying hematological malignancies. Identifying specific ocular signs associated with these disorders may aid in early diagnosis and prompt intervention, potentially improving patient outcomes. It can also help to improve clinician's ability to recognize these signs as part of a broader diagnostic workup. This may be particularly valuable for ophthalmologists and hematologists who observe patients with unexplained ocular symptoms, also study can contribute to more comprehensive treatment strategies that address both systemic and ocular health, ultimately supporting a more holistic approach to patient care.

Methodology:

This study is a retrospective observational study carried out in a Southern Punjab's tertiary care hospital's department of Ophthalmology and Hematology between March 2022 and February 2023. Prior to the study institutional ethical committee approval was secured (ERC/MBBS/SZMCH/02/2022/Ophthalmology). Prior to their enrollment in the study, each patient provided written informed consent. In case if the involved individuals were under the age of 18, parental/guardian consent was obtained. The study included all newly diagnosed and previously diagnosed (while receiving treatment) cases of leukemia, lymphoma, multiple myeloma, and plasma cell dyscrasia who visited the Department of Ophthalmology between March 2022 and February 2023. There was no limit of age and no gender exception. Participants in the study who had systemic conditions such as cardiovascular disease (CVD), diabetes, hypertension, autoimmune diseases, chronic liver disease (CLD), human immune deficiency virus (HIV) positive, cataracts or history of intra-ophthalmic surgery within previous six (6) months were excluded from the study.

To confirm the diagnosis of malignant blood disorders we evaluated the patients by taking complete picture of blood (CP), peripheral blood smear examination, biopsy examination of bone marrow,

histo/pathologic study and immunocytochemistry.[10] Brief history of demographic information was obtained and recorded for all patients. Best corrected visual acuity by using Snellen's chart was calculated and recorded. Detailed examination of anterior segment was performed with the help of slit lamp and eye movements in nine cardinal gazes were also examined. Intra-ophthalmic pressure to rule out glaucoma was assessed using applanation tonometer by Goldmann. 10% phenylephrine and 1% tropicamide mixture was used to obtain dilation of eyes in order to examine the fundus and retina. Posterior segment examination was performed with 78 D and indirect ophthalmoscope using 20 D adjusted fundoscope. Pictures of both anterior and posterior segment were taken for records and study purpose. Raosoft.Inc sample size calculator was used to calculate sample size as it is recommended for sample size greater than 30 samples.[11] With 95% confidence interval, a sample size of 90 patients was declared satisfactory.

Depending on the data, continuous variables were displayed as either the mean (± standard deviation) or the median. Statistical package for social sciences (SPSS-24) software version 24 by IBM was used. For statistical analysis one way analysis of variance (ANOVA) and Independent*t*-test were applied. P value of $\leq$ 0.05 was appraised as statistically significant. Multivariable logistic regression analysis was also performed after obtaining P values to find out any possible inter-relation among hematological parameters and ophthalmic findings of researched diseases.

Results:

Ninety (90) cases of malignant blood disorders, either newly diagnosed or undergoing treatment, were included in this study. The cases had an average age of 39.35 ± 17.44 years (range: 9–70 years). Age bracket of 19–35 years was most affected with maximum number of patients. Malignant blood disorders noted in frequency of order were leukemia (74 cases, 82.22%), lymphoma (08 cases, 8.88%), and multiple myeloma (8 cases, 8.88%) (Table No 1). Majority of cases were referrals from hematology department for ophthalmic assessment with a notable count of Eighty six (86) patients out of 90. The number of patients who directly visited the ophthalmology department prior to the diagnosis of malignant blood disorders was very minimal with a total count of four (4) patients out of ninety (90).

Table No 1: Association of malignant blood disorders and age groups

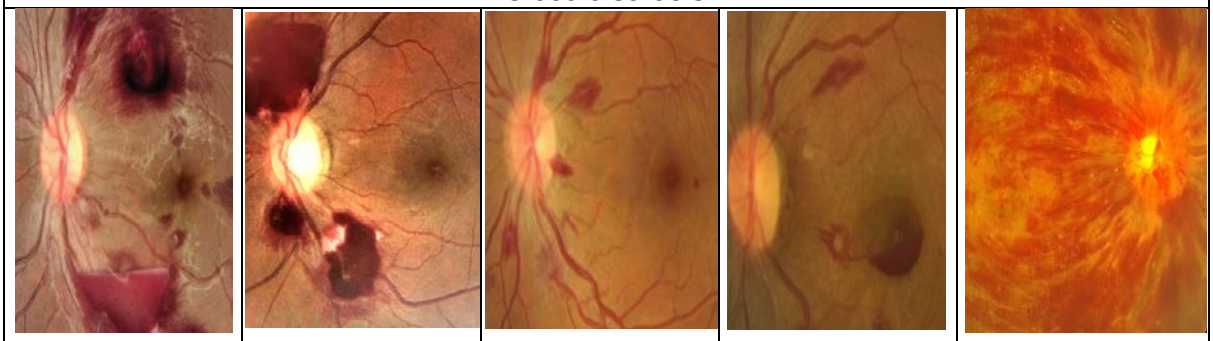
Age ranges	ALL (*n*=32)	CML (*n*=20)	AML (*n*=22)	Lymphoma (*n*=8)	MM (*n*=8)
<18 years	13 (40.62%)	0	4 (18.18%)	1 (12.50%)	0
19–35 years	13(40.62%)	11(55.00%)	11(50.00%)	4(50.00%)	1(12.50%)
36–55 years	6 (18.75%)	6 (30.00%)	7 (31.81%)	2 (25.00%)	5 (62.50%)
>56 years	0	3 (15.00%)	0	1 (12.50%)	2 (25.00%)

ALL: Acute lymphocytic leukemia; CML: chronic myeloid leukemia; AML: Acute myeloid leukemia; MM: Multiple myeloma

Images taken during the study provide a reasonably good idea of involvement of ocular tissue in malignant blood disorders. More or less all the malignant blood disorders showed similar pictures of variable intensity except Multiple Myeloma which showed numerous micro-bleeds and cotton wool spots.

(Figures (1) A, B, C, D & E)

Figure 1 (A,B,C,D & E) showing various ocular pathologies of fundus related to malignant blood disorders



A-Acute lymphocytic leukemia	B-Acute myeloid leukemia	C-Chronic myeloid leukemia	D- lymphoma	E- Multiple Myeloma

Figure A: Acute lymphocytic leukemia with massive intra-retinal hemorrhage.
Figure B: Acute myeloid leukemia with moderate intra-retinal hemorrhage.
Figure C: Chronic myeloid leukemia with moderate cotton wool spots.
Figure D: Lymphoma with mild cotton wool spots.
Figure E: Multiple myeloma with severe micro-bleeds and cotton wool spots.

Pathological findings in anterior segment were minimal around eleven (11) cases, nevertheless still not avoidable. With staggering number of pathological findings the posterior segment signs were dominant with around sixty seven (67) cases. Sub-conjuctival hemorrhage was found in eleven (11) cases in the examination of anterior segment. In decreasing frequency order the most frequent findings in posterior segment were intra-retinal hemorrhage thirty five (35) cases, at second we had pre-retinal hemorrhage sixteen (16) cases. (Table No 2- Malignant blood disorders and associated ophthalmic findings).

Table No 2: Malignant blood disorders and associated ophthalmic findings

Anterior segment					
Ophthalmic findings	ALL (n=32)	CML (n=20)	AML (n=22)	Lymphoma (n=8)	Multiple Myeloma(n=8)
Sub-conjuctivalHemorrhage	4	2	2	2	1
Normal	28	18	20	6	7
Posterior segment					
Intra-retinal Hemorrhage	13	9	10	1	2
Pre-retinal Hemorrhage	7	3	4	2	-
Cotton-wool spots	4	3	1	-	2
Retinal detachment Exudative	4	1	1	-	-
Normal	4	6	6	5	4

ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloidleukemia; MM: Multiple myeloma.

In order to find out any possible correlation among hematologic parameters of malignant blood disorders and ophthalmic pathologies we applied multivariable logistic regression analysis, the outcome variable for the multivariable logistic regression analysis was the presence of ocular pathology, coded as a binary variable (1 = presence of ocular pathology, 0 = absence of ocular pathology). This coding allowed for the examination of associations between various malignant blood disorders and the likelihood of ocular pathology, while adjusting for other covariates. Results demonstrated statistically significant correlation of total white cell count (TWCC) (p = 0.031) and total thrombocyte count (TTC) (p = 0.046) with ophthalmic pathologies (Table No 3). (Note: our dataset was not having large number of predictors/variables so we avoided univariate analysis).

Table No 3: Association of Hematological values with ophthalmic pathologies. (Multivariable logistic regression analysis)

Variables	Adjusted odds ratio (95% CI)	P- Value
TRBCC	0.39(0.15-1.10)	0.239
Hemoglobin	1.06(0.65-1.20)	0.700
TTC	0.994(0.980-0.995)	0.046
TWCC	1.065(1.002-1.002)	0.031

TRBCC: Total red blood cell count; TWCC: Total white blood cell count; TTC: Total thrombocyte count

Discussion:

In order to find a relation between malignant blood disorders and ophthalmic findings we thoroughly examined ninety (90) patients over the span of our research. The age distribution of the research population was 09–70 years old, with a mean (± SD) age of 39.35 ± 17.44 years, this is similar to the mean age of 39.73 ± 22.1 years and 41.62 ± 19.50 years that *Koshy J et al* and *Dhasmana R et al* reported respectively.[12,13]In agreement to the research by *Bukhari ZM et al.*, ours found that leukemia (ALL) and lymphoma were more common in younger age groups (<18 and 19-35 years of age), while multiple myeloma was primarily seen in 36-55 years of age.[14]According to our research, leukemia was the most common malignant blood disorder observed, with multiple myeloma and lymphoma following closely behind with similar frequencies, as reported by *Eze BI et al*.[15]In the current study, ophthalmic signs were present in 74.44% cases of malignant blood disorders, this is comparable to the 35.4% prevalence reported in a study by *Reddy SC et al* and the 43.8% prevalence reported in another study by *Bouazza M et al.*[16, 17]

It was observed that 67 cases (74.44%) had posterior segment ocular pathologies, whereas eleven (11) cases (12.22%) had anterior segment ocular pathologies. It was not uncommon to see multiple symptoms in one or both eyes. Acute leukemia was the most common cause of anterior segment symptoms.In 12.22% of cases,

there was anterior segment pathology of sub-conjunctival hemorrhage.In our study, posterior segment pathologies predominated, especially in leukemic subjects.We observed various pathologies, the most common of which were intra-retinal hemorrhages, pre-retinal hemorrhages and cotton-wool spots. Fairly identical observations were reported by *Rangel CM et al* in their study.[18] Increased total white cell count (TWCC) and decreased total thrombocyte count (TTC) values have been linked to an increased incidence of ophthalmic pathologies. Statistically both parameters showed significant p-value of(*p*-0.046) and (p-0.031) respectively. Hemoglobin's decreased mean value and decrease total red blood cell count (TRBCC) (p>0.05) showed no statistically significant association with development of ocular pathologies. Similar findings have been found in other studies, such as *Laimon DN et al.*'s study titled as "Highlights of ophthalmological manifestations in newly diagnosed acute leukemia: a correlation of hematologic parameters".[19] The most noticeable posterior segment pathologies of malignant blood disorders were retinal hemorrhages and cotton-wool spots. Cotton-wool spots appear when pre-capillary arterioles are blocked, causing retinal ischemia and retinal hemorrhages, which are linked to thrombocytopenia. This study has demonstrated that ophthalmic pathologies in patients of malignant blood disorders have significant correlation with decrease total thrombocyte count (TTC) and increased total white cell count (TWCC) and reasonably identical results were documented by *Thareja J et al.*[20]The blood parameters that were found to be significant predictors of ophthalmic manifestation on multivariable logistic regression analysis were total white cell count (TWCC) (with p-value of 0.031) and total thrombocyte count (TTC) (with p-value of 0.046). Adjusted odds ratio of multivariable logistic analysis revealed that chances of the occurrence of ophthalmic pathologies raised by 1.065 times (AOR: 1.065; 95% CI) with each unit (i.e. 1000/µL) rise in total white cell count (TWCC), on contrary the chances of the occurrence of ophthalmic pathologies declined by 0.35% (AOR: 0.994; 95% CI) with each unit (i.e. 1000/µL) rise in total thrombocyte count (TTC), these findings of present study are in agreement with *Soman S etal'*sstudy.[21]

Few limitations were noticed with current study, small demographic group was selected, even though this sample size was adequate but still a larger number of the cases would have produced more reliable results, this is a dual centeredhospital basedcross-sectional research and larger number of participating hospitals and health care providers would have provided benefit of more specific and reliable results. Severity or stage of diseases was not considered in this research and this may be considered as shortcoming of the research work.

Conclusion:

Present study demonstrates a strong association between malignant blood disorders and the prevalence of ocular pathologies, highlighting the importance of routine ophthalmologic evaluations in patients with these conditions. The findings suggest that early detection and management of ocular complications could play a critical role in improving the quality of life and outcomes for patients with malignant blood disorders. Further research is warranted to explore the underlying mechanisms and to establish clinical guidelines for integrating ophthalmologic assessments into standard care for this patient population.

Conflicts of interest: All authors declare no conflicts of interest.

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