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ORIGINAL RESEARCH

Secondary Ocular Manifestations in Acute Leukemia: Clinical Patterns and Hematologic Correlates

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Objective: To explore the clinical manifestations of secondary ocular changes in acute leukemia, classify these based on disease progression, investigate the etiology and treatment options for this rare retinal disease, and provide references for clinical management.

Methods: This cohort study was conducted in collaboration between the Department of Ophthalmology and Hematology at Beijing Friendship Hospital, Capital Medical University. A total of 74 acute leukemia patients admitted to the Hematology Department from January 2018 to September 2023 were enrolled. Ocular screenings were performed, and 34 patients with ocular symptoms were categorized and followed up. Clinical data differences were statistically analyzed based on hematologic diagnosis, and ocular manifestations and treatment outcomes were observed to identify optimal treatment approaches.

Results: Among the 74 patients, 34 (45.9%) exhibited ocular manifestations, with the majority being retinal changes (91.2%), mainly retinal hemorrhage or vascular occlusion. Ocular involvement in AML and ALL patients was classified into three severity levels, each corresponding to different treatments. Red blood cell hematocrit, white blood cell count, and platelet count were compared between AML and ALL patients with and without ocular involvement. Results showed that AML and ALL patients with retinal hemorrhage had lower hematocrit than those without ocular involvement ($P<0.05$). Platelet counts were higher in AML and ALL patients with Roth spots than in those without ocular involvement ($P<0.05$).

Conclusion: Acute leukemia remains a rare condition in ophthalmology practice in China. This study fills a diagnostic gap, providing valuable theoretical support for clinicians in terms of etiology, clinical manifestations, and treatment strategies.

Keywords: acute leukemia, secondary ocular manifestations, retinal vascular lesions, clinical treatment

Introduction

Leukemia is a group of hematologic malignancies originating from white blood cells (WBC) due to abnormal clonal proliferation of hematopoietic stem cells. It can be classified into acute and chronic leukemia. Acute leukemia is further divided into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). The most commonly used classification system for acute leukemia in clinical practice is the FAB classification.[1] The clinical manifestations of acute leukemia may vary depending on the classification, with common symptoms including anemia, infections, bleeding, and organ infiltration.[2] A previous study indicated that nearly half of acute leukemia patients experience ocular involvement.[3]

Ocular symptoms in leukemia patients may be the initial presentation or occur during chemotherapy or transplant periods. These symptoms can vary due to the different classifications of blood cell abnormalities. Ocular involvement in leukemia can result from direct leukemia infiltration or secondary involvement due to blood-related abnormalities. Blood system abnormalities include anemia, thrombocytopenia, leukocytosis, or issues related to chemotherapy or immunosuppression.[4] Direct leukemia infiltration may involve the orbit, anterior segment, uvea, and optic nerve, causing symptoms such as proptosis, cranial nerve palsy, or optic disc edema. Secondary ocular manifestations mainly consist of

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retinal changes, including retinal hemorrhage, pre-retinal or vitreous hemorrhage, infection, and retinal vascular occlusion.[5] In some leukemia patients, ocular signs may precede systemic symptoms, aiding in the early diagnosis of systemic leukemia. Due to the severity of the disease and certain factors (such as transplant periods or critical illness requiring bed rest), leukemia patients often cannot visit ophthalmology in time. As a result, ophthalmologists encounter relatively few leukemia cases, and when investigating the cause, blood system screening is often overlooked. Even when a connection between ocular manifestations and leukemia is established, patients are frequently referred directly to hematology due to a lack of diagnostic experience, missing the opportunity for timely ocular treatment. At present, studies on ocular manifestations of leukemia in China are mainly limited to case reports, with no large-scale follow-up or further treatment protocols.[6] Therefore, in collaboration with the Hematology Department of our hospital, this study was conducted by collecting acute leukemia patients admitted to the Hematology Department over the past five years. Among the patients included in this study, the majority were young adults. After undergoing hematopoietic stem cell transplantation or chemotherapy, their general condition stabilized, and at this stage, the prognosis of secondary ocular diseases may become a key factor affecting the quality of life in acute leukemia patients. This article primarily reviews the secondary ocular manifestations caused by acute leukemia and shares personal experiences in treating leukemia-related ocular diseases.

Materials and Methods

General Information

This cohort study was conducted at the Department of Ophthalmology, Beijing Friendship Hospital, Capital Medical University. The study was approved by the hospital's ethics committee (No: MR-11-24-055292) and followed the ethical principles outlined in the Helsinki Declaration, with informed consent obtained from all patients. The study began in January 2018 and will continue to collect more patients for analysis until September 2023. The study included acute leukemia patients aged 15 years and older who were hospitalized in the Hematology Department of Beijing Friendship Hospital, had been diagnosed with leukemia, and underwent immunophenotyping of blood cells via flow cytometry for FAB classification. Complete blood count and biochemical tests were also performed. Exclusion criteria included patients under 15 years old and those with a history of diabetes, acquired immunodeficiency syndrome (AIDS), sickle cell disease, or retinal vascular diseases.

Research Methods and Observational Indicators

Patients underwent a comprehensive eye examination, including assessment of visual acuity, intraocular pressure, slit-lamp biomicroscopy to evaluate the anterior segment, and direct or indirect fundus examination after pupil dilation. For patients with fundus abnormalities, further investigations were performed, including wide-field color fundus photography, ocular color Doppler ultrasound, and optical coherence tomography (OCT) when the patient's condition allowed. Once results were obtained, data were analyzed, and ocular conditions were classified into three levels: mild, moderate, and severe. Mild manifestations included pre-retinal hemorrhage, Roth spots, cotton wool spots, vascular tortuosity and dilation, macular edema, and retinal vessel sheathing. Moderate manifestations included proliferative retinal changes, retinal vascular (venous or arterial) occlusion, and vitreous hemorrhage. Severe manifestations included optic disc infiltration, exudative retinal detachment, choroidal infiltration, and hemorrhage. Based on ocular severity and the patient's overall condition, different treatment approaches were applied. Follow-up was conducted one week, one month, and three months after initial screening. During follow-up, consultations were held between the Hematology and Ophthalmology departments. Ophthalmology routinely performed wide-field color fundus photography, and Hematology performed routine blood system tests. Blood routine data were collected from all confirmed patients at the time secondary ocular changes first appeared. Representative indicators were selected to compare blood routine abnormalities between the symptomatic group and the control group, in order to explore the correlation between fundus manifestations and systemic blood cell parameters and make a preliminary judgment on the etiology.

Statistical Analysis

SPSS version 22.0 was used for data analysis. Descriptive variables were presented as frequency and percentage, while quantitative variables were expressed as mean (SD) ± standard deviation. The comparison of quantitative blood routine variables was performed using independent sample *t*-tests to assess the effect of blood routine parameters on ocular manifestations ($P<0.05$ was considered statistically significant).

Results

General Information

A total of 74 patients were included in the study, comprising 47 males (63.5%) and 27 females (36.5%), with a male-to-female ratio of 1:1.74. Among the patients, 30 (40.5%) were diagnosed with acute lymphoblastic leukemia (ALL), and 44 (59.5%) with acute myeloid leukemia (AML). Ocular manifestations were observed in 34 patients (45.9%) of the total cohort, with retinal changes accounting for the vast majority (91.2%). Among these patients, 21 (61.8%) were male, and 13 (38.2%) were female. Ocular involvement was more common in AML patients (67.6%) (Table 1). It is noteworthy that ocular manifestations were not necessarily present during the initial ophthalmologic screening. In 16 patients (47.05%) with ocular changes, the fundus abnormalities were detected only during subsequent hospitalizations for treatment and follow-up ophthalmic screenings.

Grading of Fundus Manifestations and Corresponding Ophthalmic Treatment Recommendations

Among the 34 patients with ocular involvement, 31 had fundus involvement, excluding two patients with orbital masses and one with corneal infection. The fundus manifestations in AML and ALL patients were categorized into three levels: mild, moderate, and severe (Table 2). Of these, 21 patients (67.7%) had mild ocular involvement, primarily presenting as vitreous hemorrhage, pre-retinal hemorrhage, Roth spots, cotton wool spots, vascular tortuosity and dilation, macular edema, retinal vascular sheathing. For these patients, oral medications were administered to promote absorption of hemorrhage, with laser therapy added when necessary. Most of the patients showed improvement or stabilization of fundus findings, with no significant impact on visual function after treatment. Additionally, some mild cases were identified during screening but did not affect vision.

Moderate fundus involvement was observed in 7 patients (22%), who exhibited proliferative retinal changes, retinal vascular (venous or arterial) occlusion, and vitreous hemorrhage in addition to mild manifestations. Fundus changes were often associated with the progression of the systemic condition. These patients were treated with appropriate oral medications to control bleeding, with hematology department-led treatment. Regular follow-ups were conducted, and

Table 1 Incidence of Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)

Leukemia Classification	Gender	Eye Manifestation		Total	x^2	P
		Yes	No			
AML(n=44)	Male	14	15	29	0.545	0.460
	Female	9	6	15		
	Total	23	21	44		
ALL(n=30)	Male	7	11	18	0.096	0.750
	Female	4	8	12		
	Total	11	19	30		
Total (n=74)	Male	21	26	47	0.083	0.773
	Female	13	14	27		
	Total	34	40	74		

Table 2 Grading of Fundus Manifestations and Corresponding Ophthalmic Treatment Recommendations for Patients with Acute Leukemia

Classification	Number of Patients (n=31)		Fundus Manifestations	Treat
	AML	ALL		
Mild	13	8	Preretinal hemorrhage, Roth spots, cotton wool spots, vascular tortuosity and dilation, macular edema and infiltration, retinal vascular sheath	Oral medications to promote hemorrhage absorption, including lecithin-iodine complexes, traditional Chinese medicine, and laser therapy if necessary.
Moderate	5	2	Proliferative retinopathy, retinal vascular (venous or arterial) occlusion, vitreous hemorrhage	Ophthalmic surgical intervention may be considered after systemic condition stabilizes.
Severe	2	1	Optic disc infiltration, exudative retinal detachment, choroidal infiltration and hemorrhage	Primary hematologic treatment, with etiology-specific therapy and laser treatment if necessary.

when the patient's condition stabilized and kidney function allowed, further interventional or invasive treatment was performed. Close attention to ocular status during the perioperative period was essential to avoid infections.

Among the enrolled patients, severe fundus involvement was seen in 3 patients (9.7%), who developed optic disc infiltration, exudative retinal detachment, choroidal infiltration, and hemorrhage in addition to mild or moderate manifestations. These patients generally had poor systemic conditions, often complicated by renal failure, and some were unable to leave their beds or cooperate with additional diagnostic procedures, making it difficult to confirm the diagnosis. Symptomatic treatment was provided, and further management was deferred until the patient's condition improved and blood routine values stabilized. However, among the patients with severe retinal disease in this study, the systemic condition had already deteriorated by the time ocular diagnosis was made, and some patients either abandoned treatment or passed away before their condition stabilized, thus precluding further ocular treatment. This highlights a unique aspect of leukemia-associated ocular disease.

Of the 31 patients with ocular involvement, 16 (50%) had impaired vision, including some with mild and all with moderate or severe involvement. Among these, 13 patients had pre-retinal hemorrhage and Roth spots, and 8 had macular involvement. During the 3-month follow-up, visual acuity testing with best corrected visual acuity (BCVA), wide-field fundus photography, and OCT revealed an average improvement of 20.5 letters in mild cases and 13.4 letters in moderate cases. In mild and moderate patients, those with macular involvement had more severe vision loss. OCT and fundus imaging identified retinal hemorrhage and Roth spots in the macular region as the main causes of visual decline.

Fundus Hemorrhage and Hematologic Changes in Acute Leukemia Patients

Given the impact of fundus hemorrhage and Roth spots on the fundus in leukemia, this study explored the underlying causes of these two major ocular manifestations. The study collected the most recent complete blood count (CBC) results of patients with fundus hemorrhage and compared them with the CBC results of patients without ocular involvement at the time of eye screening, aiming to identify parameters associated with fundus hemorrhage. Based on literature reports and a small sample estimation, the final parameters selected for analysis were hematocrit, white blood cell count, and platelet count. Hematologic parameters were statistically analyzed for AML and ALL patients with and without ocular involvement (Table 3). Independent sample *t*-tests using SPSS 26.0 software revealed that AML and ALL patients with ocular involvement had lower hematocrit levels, which were statistically significant when compared to those without ocular involvement (AML: $P<0.05$, $t=-5.493$; ALL: $P<0.05$, $t=-3.853$; AML+ALL: $P<0.05$, $t=-6.152$). No statistically significant differences were found in the white blood cell count or platelet count between patients with ocular involvement and those without ocular involvement.

Figure 1 illustrates the case of a 29-year-old male patient diagnosed with acute myeloid leukemia (M4 type) who was scheduled for bone marrow transplantation. During routine screening, retinal hemorrhage was detected, and various

Table 3 Fundus Hemorrhage and Changes in the Blood System in Patients with Acute Leukemia

Hematological Parameters		n	Hematocrit (%)	White Blood Cell Count($\times 10^9$)	Platelet count($\times 10^9$)
AML(n=43)	Eyes affected	20	21.70±4.70*	58.98±7.87	26.43±6.63
	Eyes not affected	23	30.90±6.26	58.72±5.97	25.15±5.98
ALL(n=28)	Eyes affected	11	18.55±4.29*	58.72±5.97	29.85±5.32
	Eyes not affected	17	25.56±4.98	67.14±6.93	31.32±5.87
Total(n=71)	Eyes affected	31	20.58±4.74*	61.88±8.43	27.64±6.33
	Eyes not affected	40	28.63±6.28	61.78±7.62	27.77±6.62
	$t_{(AML)}$		−5.493	0.121	0.661
	$P_{(AML)}$		<0.05	>0.05	>0.05
	$t_{(ALL)}$		−3.853	0.433	−0.687
	$P_{(ALL)}$		<0.05	>0.05	>0.05
	$t_{(AML+ALL)}$		−6.152	0.049	−0.084
	$P_{(AML+ALL)}$		<0.05	>0.05	>0.05

Note: * indicates that compared with the same group without eye involvement, P<0.05.

ophthalmic examinations were performed. The figure shows his condition at the initial screening and follow-up after treatment.

Roth Spots and Hematologic Changes in Acute Leukemia Patients

This study also analyzed the complete blood count (CBC) results at the most recent time point when Roth spots were first detected in patients with ocular involvement. Similarly, hematocrit, white blood cell count, and platelet count were selected for comparison with the results from patients without ocular involvement (Table 4). Independent sample *t*-tests

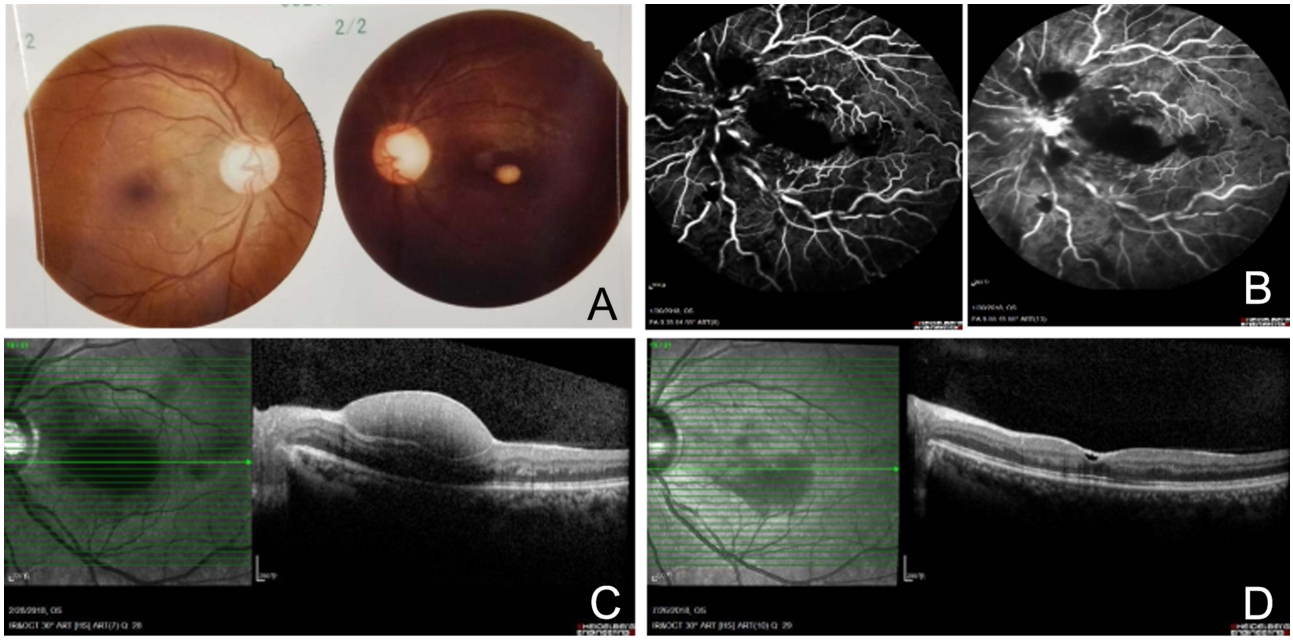

Figure 1 Retinal changes in a 29-year-old male with acute myeloid leukemia during initial screening and after treatment. (**A**) At the initial screening, the patient's visual acuity was V: R: 1.2; L: 0.2, with fixed exotropia in the left eye. Retinal flat hemorrhages and Roth spots in the macular area were observed. The fundus was graded as mild retinal disease. Platelet count at the initial screening was $35*10^9$. (**B**) Early fluorescein angiography (left) showed tortuous and dilated retinal vessels in the left eye, with a patchy fluorescence blockage in the hemorrhagic area. In the late phase (right), high fluorescence in the optic disc with fluorescence leakage was observed. (**C**) Optical coherence tomography (OCT) of the macula at the initial screening revealed macular infiltration, disappearance of the foveal shape, uniform, non-layered infiltration lesions, and macular thickening with a dome-shaped appearance. (**D**) After five months of symptomatic treatment and bone marrow transplantation, the patient's blood cell levels normalized, retinal hemorrhage was absorbed, and Roth spots regressed. Follow-up OCT showed the macular area had restored its basic shape, although a macular pucker developed. Best corrected visual acuity was 0.8, and exotropia gradually improved due to continuous vision correction during treatment.

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Table 4 Roth Spots and Changes in the Blood System in Patients with Acute Leukemia

Hematological Parameters		n	Hematocrit (%)	White blood Cell Count($\times 10^9$)	Platelet count($\times 10^9$)
AML(n=43)	Eyes affected	16	25.87±8.46	58.07±7.22	31.78±4.01*
	Eyes not affected	27	26.87±6.59	59.30±6.70	22.04±4.19
ALL(n=28)	Eyes affected	10	25.50±3.64	66.22±6.70	36.61±2.92*
	Eyes not affected	18	24.47±5.33	66.51±7.81	27.49±3.72
Total(n=71)	Eyes affected	26	26.87±6.59	59.21±7.98	27.99±4.29*
	Eyes not affected	45	25.08±6.17	61.14±7.93	25.87±4.80
	$t_{(AML)}$		−0.549	−0.553	7.581
	$P_{(AML)}$		>0.05	>0.05	<0.05
	$t_{(ALL)}$		0.606	−0.104	7.168
	$P_{(ALL)}$		>0.05	>0.05	<0.05
	$t_{(AML+ALL)}$		−0.111	−0.499	8.531
	$P_{(AML+ALL)}$		>0.05	>0.05	<0.05

Note: * indicates that compared with the same group without eye involvement, P<0.05.

revealed that platelet counts in AML and ALL patients with ocular involvement were statistically significant (AML: P<0.05, t=7.581; ALL: P<0.05, t=7.168; AML+ALL: P<0.05, t=8.531).

Discussion

Leukemia is a malignant bone marrow tumor that can affect multiple organs, including the eyes. Ocular involvement in leukemia is very common, with reported prevalence ranging from 9% to 90% in various studies.[7] This variation may stem from differences in physician attention or changes in ocular effects with blood cell counts. Ocular involvement is most frequently observed in acute leukemia. In this study of 74 patients, no significant differences in ocular involvement were found between leukemia types or genders. However, male patients (63.5%) were more common than female patients (36.5%), which aligns with previous literature.[8]

In this study, 45.9% of acute leukemia patients showed ocular involvement, with 41.9% presenting with fundus changes. Retinal involvement was the most frequent manifestation, particularly retinal hemorrhage, corroborating previous studies.[9] Among 34 patients with ocular involvement, 16 (47%) had vision impairment, with retinal hemorrhage and macular infiltration being the primary causes of vision loss. OCT and fundus photography revealed that macular infiltration occurs in 39% to 53% of acute leukemia patients with fundus involvement.[10]

Ocular involvement in acute leukemia can indicate a poorer prognosis or disease relapse,[11] highlighting the importance of collaboration between hematologists and ophthalmologists for initial screening and follow-up.

Through grading the disease severity of enrolled patients and applying corresponding treatment strategies, it was observed that retinal hemorrhage and Roth spots were the two major fundus manifestations, both closely associated with hematological abnormalities. The analysis of hematological data is critically important for understanding the etiology, clinical presentation, and treatment of fundus changes in acute leukemia.

Relationship Between Retinal Hemorrhage and Hematological Parameters

The main clinical manifestations of acute leukemia include anemia, fever, bleeding, lymphadenopathy, and hepatosplenomegaly. The primary causes of anemia are reduced production of mature erythrocytes, ineffective erythropoiesis, and hemolysis. The pathogenesis of anemia is closely related to hemorheology. Macroscopically, hemorheology is evaluated by whole blood viscosity, which is associated with hematocrit, plasma viscosity, red blood cell deformability, and fibrinogen levels. Among these factors, hematocrit is the most important. Therefore, this study selected hematocrit as the representative parameter to explore the impact of hemodynamics on retinal hemorrhage.

In this study, the incidence of fundus hemorrhage was higher in patients with AML (46.51%) than in those with ALL (39.29%), consistent with previous studies. The relationship among retinal hemorrhage, hematocrit, and platelet count

has been a recent focus of acute leukemia research. A prospective study on leukemic retinopathy indicated that patients with ALL and retinal hemorrhage had lower hematocrit levels than those without hemorrhage,[12] while leukocyte count was unrelated to the presence of hemorrhage.[13] Isolated thrombocytopenia was not associated with an increased risk of retinal hemorrhage,[14] but patients with both severe anemia and thrombocytopenia were more likely to develop retinal hemorrhage, suggesting that hematocrit is the true determinant. It has been reported that for every 10 g/L increase in hemoglobin concentration, the risk of clinically significant bleeding the following day decreases by 22%. Moreover, bleeding time was negatively correlated with hematocrit levels.[15] These findings highlight that hematocrit is a key factor contributing to bleeding in leukemia patients. Retinal hemorrhage may thus reflect a systemic bleeding tendency, warranting close attention to prevent serious cardiovascular and cerebrovascular events. Nevertheless, the precise mechanisms by which hematocrit induces hemorrhage are still under investigation.[16]

Relationship Between Roth Spots and Hematological Parameters

Roth spots refer to hemorrhagic lesions in the retina with a white central spot. They can be seen in both infectious and non-infectious diseases. Infectious Roth spots, commonly observed in infective endocarditis, feature microabscesses at their center. Non-infectious Roth spots, as seen in acute leukemia, are characterized histopathologically by capillary rupture and fibrin-platelet thrombus formation.

Leukemia-related Roth spots located in the peripheral retina typically have minimal effects on vision, whereas those in the macular area, termed macular infiltration,[17] can significantly impair visual acuity. Their formation is attributed to abnormal proliferation of blood cells, increased intravascular pressure, ischemia, and enhanced capillary fragility, leading to dysfunction and rupture of retinal capillary endothelial cells. Platelets adhere to the damaged endothelium, activating the coagulation cascade and eventually forming fibrin-platelet thrombi.[18–20] Therefore, in this study, the platelet count in patients with Roth spots was significantly higher compared to controls, with statistical significance.

OCT analysis of macular infiltrations indicated that leukemic retinal hemorrhages occurred at the intraretinal and sub-ILM levels, consistent with previous findings.[21] Clinically, the macular foveal depression disappeared, replaced by a homogeneous infiltrative lesion without distinct stratification, macular thickening, and a dome-shaped morphology. Mild destruction of the macular retinal structure was observed (Figure 1). According to the literature, changes in retinal blood flow in the macular area also contribute to this phenomenon. OCTA revealed increased reflectivity of the retinal vessel walls in the macular region, likely due to disrupted hemorheology caused by hyperviscosity in leukemia.[22] For patients with good baseline vision, macular infiltration often results in sudden vision loss or even monocular strabismus.

Long-term follow-up showed that macular Roth spots were reversible. After hematological parameters normalized through bone marrow transplantation or chemotherapy, the hemorrhages and leakage in the macular region gradually resolved, leading to improved visual acuity. However, some structural damage remained, such as generalized thinning of the macular retina, and the degree of visual recovery varied depending on the disease status and patient age. More detailed data supporting these findings will be provided in future studies. Therefore, patients with macular infiltration should be managed proactively, maintaining hematological homeostasis to minimize retinal damage. Although Roth spots adversely affect vision, this study's data suggest that platelet counts in affected patients tended to approach normal levels, potentially indicating a favorable prognosis.[23]

For patients presenting with retinal hemorrhage at initial diagnosis, in addition to evaluating blood glucose, blood pressure, and hemodynamic parameters, routine blood tests should be incorporated into standard screening. If hematological abnormalities are detected, prompt consultation with hematologists for leukemia diagnosis and fundus examination for grading and treatment initiation are essential. Follow-up at three months revealed that disease severity could be influenced by external factors such as chemotherapy, transplantation, and postoperative complications. Chemotherapy suppresses normal stem cell and mature blood cell proliferation in the bone marrow, while post-transplant hematopoietic recovery typically takes up to three years. Therefore, intensified monitoring is recommended during predictable systemic changes to detect disease progression early and implement timely interventions. Caution should be exercised with invasive procedures such as fluorescein angiography or surgical interventions to prevent life-threatening infections. Overall, after disease grading and targeted treatment, patients exhibited varying degrees of visual improvement, closely tied to their overall systemic health status.

This study has several limitations. First, it is a retrospective single-center study, limiting generalizability. Future multicenter collaborations are needed to enhance the robustness of findings. Second, selection bias may exist, as the study included patients with relatively stable systemic conditions who could cooperate with examinations. Critically ill patients with rapid disease progression were often excluded, possibly underestimating the actual prevalence of fundus abnormalities. Third, disease grading relied on the clinical judgment of observers, introducing some subjectivity. In this study, two experienced ophthalmologists independently graded the fundus findings, with discrepancies resolved by a senior specialist to minimize error. Lastly, the sample size was relatively small, limiting the ability to account for confounding variables such as age, leukemia subtype, and disease stage. Future studies should further refine these variables to obtain more objective results.

Conclusion

Leukemia-related ocular changes are still underexplored in China. This study suggests that all acute leukemia patients should undergo mandatory ophthalmologic screening at diagnosis. The progression of ocular involvement is closely tied to blood cell levels and can affect vision, providing valuable insight into prognosis. Ophthalmologists should work closely with hematologists to monitor and manage ocular changes in leukemia patients.

Ethics Statement

The study was approved by the Beijing Friendship Hospital's ethics committee (No: MR-11-24-055292) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Disclosure

The authors report no conflicts of interest in this work.

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