European Journal of Ophthalmology / Vol. 18 no. 4, 2008 / pp. 619-623

# Orbital and ocular manifestations of acute childhood leukemia: Clinical and statistical analysis of 180 patients

*V. RUSSO[1], I.U. SCOTT[2], G. QUERQUES[1], A. STELLA[1], A. BARONE[1], N. DELLE NOCI[1]*

[1]Institute of Ophthalmology, University of Foggia, Foggia - Italy
[2]Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, PA - USA

PURPOSE. *To investigate the association between presence of orbital or ocular lesions and type and stage of leukemia and to investigate whether orbital and ocular lesions are significant in predicting leukemia prognosis.*

METHODS. *The authors evaluated 180 patients with acute childhood leukemia. Lesions associated with leukemia may be classified as specific (due to leukemic infiltration of various ocular tissues), nonspecific (due to one of the secondary complications), or iatrogenic manifestations caused by chemotherapy. Risk-based treatment assignment is based on clinical and laboratory features at diagnosis. Children with presenting white blood cell count below 50,000 mm$^3$ are considered at standard risk for treatment failure, while all others are considered at high risk for treatment failure.*

RESULTS. *Specific lesions were noted in 66% of patients with acute myeloid leukemia (AML) and 11.5% patients with acute lymphocytic leukemia (ALL) ($p<0.05$), and were more severe in patients with high risk leukemia than in patients with standard risk leukemia. Orbital or ocular lesions were noted more commonly in patients with AML (66.6%) compared to patients with ALL (15.1%). In both the AML and ALL groups, there was a higher frequency of leukemic relapses in the bone marrow and/or central nervous system in patients with specific lesions (63.1%) compared to patients with nonspecific lesions (42%), and in patients without orbital or ocular lesions (29.2%) ($p<0.05$).*

CONCLUSIONS. *In both the AML and ALL groups, the presence of specific orbital or ocular lesions was associated with a higher frequency of bone marrow relapses and CNS involvement ($p<0.05$), leading to a lower survival rate. (Eur J Ophthalmol 2008; 18: 619-23)*

KEY WORDS. *Acute childhood leukemia, Ocular manifestation, Orbital manifestation, Survival rate*

*Accepted: January 16, 2008*

## INTRODUCTION

Leukemia is caused by the malignant transformation of hematopoietic cells. Leukemic cells proliferate in the bone marrow and lymphoid tissue and then migrate to the peripheral blood and infiltrate other tissues. The classification of childhood leukemias is based on the predominant cell line affected and the level of cellular differentiation. The three major classifications of childhood leukemia are acute lymphocytic leukemia (ALL), accounting for 75% to 80% of childhood leukemia, acute myelogenous leukemia (AML), accounting for 20% to 25% of childhood leukemia, and chronic myelogenous leukemia, accounting for less than 5% of childhood leukemia (1). AML and ALL have a rapid clinical course and usually are fatal within a few months if not treated (2, 3).

Orbital and ocular lesions are the third most frequent extramedullary location of acute leukemia after the meninges and testicles (4) and may be the presenting features of the disease (5). Intraocular manifestations of

 1120-6721/619-05$25.00/0

leukemia may be caused by the accumulation of circulating leukemic cells in the uvea, retinal nerve fibers, optic disc, and other intraocular tissues and fluids (6). Intraocular manifestations may also be caused by hematologic disorders associated with leukemia such as thrombocytopenia, anemia, and hyperviscosity causing ischemia or by opportunistic infections (7).

Intraocular manifestations include vitreous cells, retinal venous congestion, optic nerve infiltration, retinal pigment epithelial detachment, non-rhegmatogenous retinal detachment, localized or diffuse choroidal infiltration, neoplastic hypopyon, infiltration of the iris, retinal hemorrhages, and white-centered retinal hemorrhages (Roth spots) (8). The typical leukemic retinal lesion is a white retinal plaque, flat and not well defined, frequently associated with retinal hemorrhages and overlying vitreous cells (9). Mono- or multifocal leukemic infiltration of the retinal nerve fibers can be present in both eyes.

Orbital and ocular lesions associated with leukemia may be classified as specific, due to leukemic infiltration of various ocular tissues (e.g., Roth spots, orbital infiltrations, and papilledema), or nonspecific as a result of one of the secondary complications of the disease (e.g., retinal hemorrhage, keratitis and conjunctivitis, blepharitis, iritis); such complications include anemia, thrombocytopenia, and leukostasis, which can lead to retinal hemorrhages and ischemia (10). Iatrogenic manifestations are those caused by chemotherapy and cobaltotherapy (11) (e.g., ptosis, choroidal and retinal atrophy, visual field changes, and ocular atrophy).

Specific lesions include orbital infiltration (causing exophthalmos and/or palpable masses along the orbital border) and, less commonly, palpebral, conjunctival, and lacrimal gland infiltrations. Anterior uveal involvement is characterized by leukemic pseudohypopyon, caused by white blood cells filtered in the anterior chamber through the iris and ciliary vessels. Choroidal infiltration appears as white-grayish subretinal lesions. Leukemic retinal lesions typically appear as retinal hemorrhages (some, known as Roth spots, contain white centers). Uveoretinal involvement is noted in approximately 70% of eyes examined histologically compared to 49% noted on clinical examination (12). Optic nerve involvement is the direct consequence of central nervous system infiltration by leukemic cells or may be due to increased intracranial pressure. In both cases, the ophthalmoscopic picture is characterized by optic nerve edema with peripapillary hemorrhages.

The aim of the current study is to investigate the association between 1) presence of orbital or ocular lesions and 2) type and stage of leukemia and to investigate whether orbital and ocular lesions are significant in predicting leukemia prognosis.

## METHODS

The study was approved by the Institutional Review Board of the University of Foggia. Medical records were reviewed of all patients evaluated at the University of Foggia with the diagnosis of acute childhood leukemia between 1984 and 2004. At the University of Foggia, all patients diagnosed with acute childhood leukemia are referred for an ophthalmologic evaluation at the Department of Ophthalmology of the University. Ophthalmologic examinations at presentation and follow-up visits included visual acuity and intraocular pressure measurements, as well as slit-lamp, dilated funduscopic examinations, and clinical and laboratory features. Leukemia type was classified according to morphologic findings, AML and ALL, and prognostic classifications as indicated by Children's Oncology Group (1). Risk-based treatment assignment is based on clinical and laboratory features at diagnosis. Children with presenting white blood cell count below 50,000 $mm^3$ are considered at standard risk for treatment failure, while all others are considered at high risk for treatment failure (1). The orbital and ocular lesions were classified as specific, nonspecific, and iatrogenic, and the associations of orbital and ocular lesions with the stage of the leukemia, the type of leukemia, and leukemia progression and survival rate were investigated (the latter was calculated using the Kaplan-Meier method).

## RESULTS

A total of 180 patients with acute childhood leukemia were identified, including 159 with ALL and 15 with AML. The study population included 91 boys and 89 girls with a median age of 8 years (range, 1-14 years); 45 patients were younger than 3 years, 120 were between 3 and 10 years, and 15 were between 10 and 14 years. Fifty-seven patients had high risk ALL, 102 had standard risk ALL, 15 had AML, and 6 patients could not be assessed because adequate written and photographic documentation was not available.

Eighty-six patients were examined at presentation, 64

under therapy, and 30 off therapy because they failed prior treatment. Table I displays the orbital and ocular lesions identified. Specific lesions were observed in 29 (16.1%) patients, nonspecific lesions in 66 (36.6%) patients, and iatrogenic lesions in 10 (5.5%) patients. Specific manifestations were observed in 11 (12.7%) patients at presentation, in 17 (26.5%) patients examined under therapy, and in 1 (3.3%) patient off therapy. The most frequent specific lesions were Roth spots, orbital infiltrations, and papilledema. Nonspecific lesions were noted in 21 (24%) patients observed at presentation, 39 (60.9%) patients under therapy, and 6 (20%) patients off therapy. Iatrogenic lesions were noted in 8 (12.5%) patients examined under therapy and 2 (6.6%) patients off therapy.

Orbital or ocular lesions were noted more commonly in patients with AML (10/15) (66.6%) compared to patients with ALL (19/159) (11.5%) ($p<0.05$), and were noted more commonly in patients with high-risk leukemia (26.3%) com-

**TABLE I -** ORBITAL AND OCULAR LESIONS

| Ocular manifestations | At presentation (n=86) | Under therapy (n=64) | Off therapy (n=30) | Total (n=180) |
|---|---|---|---|---|
| Specific | | | | |
| Papilledema | 3 (3.4%) | 2 (3.1%) | | 5 (2.7%) |
| Roth spots | 2 (2.3%) | 5 (7.8%) | | 7 (3.8%) |
| Leukemic hypopyon | | 3 (4.6%) | | 3 (1.6%) |
| Optic nerve infiltration | | 2 (3.1%) | | 2 (1.1%) |
| Exophthalmos | 5 (5.8%) | | 1 (3.3%) | 6 (3.3%) |
| Optic pallor | 1 (1.1%) | 1 (1.5%) | | 2 (1.1%) |
| Retinal infiltrations | | | | 0 |
| Vitreal opacities | | 2 (3.1%) | | 2 (1.1%) |
| Total | 11 (12.7%) | 17 (26.5%) | 1 (3.3%) | 29 (16.1%) |
| Nonspecific | | | | |
| Retinal hemorrhage | 7 (8.1%) | 2 (3.1%) | | 9 (5%) |
| Venous congestion | | 3 (4.6%) | | 3 (1.6%) |
| Keratitis | | 5 (7.8%) | | 5 (2.7%) |
| Blepharitis | | 1 (1.5%) | | 1 (0.5%) |
| Subconjunctival hemorrhage | 3 (3.4%) | 3 (4.6%) | 6 (3.3%) | |
| Palpebral edema | 8 (9.3%) | 3 (4.6%) | 3 (10%) | 14 (7.7%) |
| Conjunctival hyperemia | 3 (3.4%) | 22 (34.37%) | 3 (10%) | 28 (15.5%) |
| Total | 21 (24%) | 39 (60.9%) | 6 (20%) | 66 (36.6%) |
| Iatrogenic | | | | |
| Chorioretinal atrophy | | 3 (4.6%) | | 3 (1.6%) |
| Ptosis | | 3 (4.6%) | | 3 (1.6%) |
| Restricted visual field | | | 2 (6.6%) | 2 (1.1%) |
| Optic nerve atrophy | | 2 (3.1%) | | 2 (1.1%) |
| Total | 0 | 8 (12.5%) | 2 (6.6%) | 10 (5.5%) |

**TABLE II -** CASE STUDIES

| | No alterations | Specific alterations | Non specific alterations | Iatrogenic alterations |
|---|---|---|---|---|
| Age, yr | | | | |
| <3 (n=45) | 17 | 5 | 20 | 3 |
| 3–10 (n=120) | 54 | 20 | 38 | 8 |
| >10 (n=15) | 2 | 4 | 8 | 1 |
| ALL high risk (n=57) | 14 | 13 (26.3%) | 25 | 5 |
| ALL standard risk (n=102) | 49 | 6 (9.3%) | 40 | 7 |
| Impossible to evaluate (n=6) 6 | | | | |
| AML (n=15) | 4 | 10 (66%) | 1 | |
| Total (n=180) | 73 | 29 | 66 | 12 |

ALL = Acute lymphocytic leukemia; AML = Acute myelogenous leukemia

**TABLE III -** EVOLUTION OF OCULAR/ORBITAL LESION DURING LEUKEMIA

| ALL + AML (n=66) | No alterations (n=85) | Specific alterations (n=29) | Nonspecific alterations |
|---|---|---|---|
| ALL (n=159) | 82 | 19 | 50 |
| Total relapses | 24 (29.2%) | 12 (63.1%) | 21 (42%) |
| Medullary relapses | 19 (23.1%) | 12 (63.1%) | 19 (38%) |
| Extramedullary relapses | 5 (6%) | | 2 (4%) |
| Early exitus | 3 (3.6%) | 3 (15.7%) | 1 (2%) |
| Living in GSH | 65 (79.2%) | 10 (52.6%) | 27 (60%) |
| Off-therapy | 24 (29.2%) | 1 (5.2%) | 14 (28%) |
| Off-therapy relapses | 9 (10.9%) | | 3 (6%) |
| AML (n=15 ) | 4 | 10 | 1 |
| Total relapses | 2 (50%) | 9 (90%) | |
| Medullary relapses | 2 (50%) | 6 (60%) | |
| Extramedullary relapses | | 3 (30%) | |
| Early exitus | | 1 (10%) | |
| Living in GSH | 3 (75%) | 1 (10%) | |
| Off therapy | 3 (75%) | 1 (10%) | |

ALL = Acute lymphocytic leukemia; AML = Acute myelogenous leukemia; GSH = Good state of health

pared to patients with standard risk (9.3%) disease ($p<0.05$) (Tab. II). There was a higher frequency of leukemic relapses in bone marrow and/or central nervous system in patients with specific orbital or ocular lesions (63.1%) compared to patients with nonspecific lesions (42%) or patients without lesions (29.2%) ($p<0.05$) (Tab. III).

Among the 159 patients with ALL, survival was greater in patients without orbital or ocular lesions (79.2%) compared to patients with nonspecific lesions (60%) and patients with specific lesions (52.6%) ($p<0.05$) (Tab. III).

## DISCUSSION

Ocular involvement during leukemia is frequent (varying from 42% to 49%), can be the result of different mechanisms, and may be the presenting feature of the disease (13). Since some authors report the presence of ocular lesions in many asymptomatic patients with leukemia, ophthalmic examination should be included as a part of the routine evaluation at initial diagnosis in these patients (14). At the time of diagnosis of acute leukemia, half of children demonstrate ocular involvement (15). Most commonly, this is due to alterations of hematologic parameters, such as elevated white blood cell count, low platelet count, and increased blood viscosity, while leukemic infiltration of the retina is less frequent.

Results of the current study provide evidence of an association between orbital or ocular lesions and type of leukemia: specific lesions were observed significantly more frequently in patients with leukemias characterized by a greater tendency to disseminate, such as AML and high-risk ALL (16, 17). The current study results also provide evidence of a significant association between presence of orbital or ocular lesions and prognosis of leukemia. There is a significant difference in the frequency of relapses noted in patients with specific or nonspecific orbital or ocular lesions (63.1% and 42%, respectively) compared to patients without orbital or ocular lesions (30.2%) ($p<0.05\%$). Since the appearance of leukemic eye manifestations often depend on abnormal hematologic indices (12), this has a negative prognostic significance, especially because this usually indicates recurrence of leukemia. Retinal, choroidal, and vitreous infiltration is usually observed in the end stages of the disease and when the central nervous system is involved (17).

The presence of specific eye lesions at presentation contributes to defining a population of leukemic patients at high risk especially of leukemic relapse in the central nervous system (18) with an associated poorer prognosis.

*None of the authors has a financial interest in the subject matter of this article.*

Reprint requests to:
Vincenzo Russo, MD, PhD
Institute of Ophthalmology
University of Foggia
Viale Luigi Pinto
71100 Foggia, Italy
virus66@inwind.it

## REFERENCES


1. Colby-Graham MF, Chordas C. The childhood leukemias. J Pediatr Nurs 2003; 18: 87-95.
2. Mathers CD, Shibuya K, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: application of regional cancer survival model to estimate cancer mortality distribution by site. BMC Cancer 2002; 2: 36.
3. Redaelli A, Laskin B, Stephens J, Botteman M, Pashos CL. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). Eur J Cancer Care 2005; 14: 53-62.
4. Charif Chefchaouni M, Belmekki M, Hajji Z, et al. Ophthalmic manifestations of acute leukemia. J Fr Ophtalmol 2002; 25: 1: 62-6.
5. Culler AM. Fundus changes in leukaemia. Trans Am Ophthalmol Soc 1951; 49: 445-73.
6. Schachat AP, Markowitz JA, Guyer DR, Burke PJ, Karp JE, Graham ML. Ophthalmic manifestations of leukaemia. Arch Ophthalmol 1989; 107: 607-700.
7. Holt JM, Gordon-Smith EC. Retinal abnormalities in disease of the blood. Br J Ophthalmol 1969; 53: 145-60.
8. Loewenstein JL. Retinopathy associated with blood anomalies. In: Albert DM, Jakobiec FA. Principles and Practice of Ophthalmology. Philadelphia: Saunders, 1994; 995-1000.
9. Schepens CL, Reagan CDJ, eds. Controversial Aspects of the Management of Retinal Detachment. Boston: Little, Brown, 1965; 6-7.
10. Mitelman F. Basel, (ed). International System for Human Cytogenetic Nomenclature (1995). Recommendations of the International Standing Committee on Human Cytogenetic Nomenclature. Memphis: Karger; 1995.
11. Leith CP, Kospeky KJ, Godwin J, et al. Acute myeloid leukaemia in the elderly: assessment of multidrug resistance (MDR) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group Study. Blood 1997; 89: 3323-9.
12. Reddy SC, Jackson N. Retinopathy in acute leukaemia at initial diagnosis: correlation of fundus lesions and haematological parameters. Acta Ophthalmol Scand 2004; 82: 81-5.
13. Dahreddine M, Karim A, Moussaif H, Essekali NH, Mohcine Z. White-centered retinal hemorrhage revealing acute lymphoblastic leukemia. J Fr Ophtalmol 2004; 27: 506-9.
14. Reddy SC, Jackson N, Menon BS. Ocular involvement in leukemia: a study of 288 cases. Ophthalmologica 2003; 217: 441-5.
15. Abu el-Asrar AM, al-Momen AK, Kangave D, Harakati MS, Ajarim DS. Correlation of fundus lesions and haematologic findings in leukaemic retinopathy. Eur J Ophthalmol 1996; 6: 167-72.
16. Guyer DR, Schachat AP, Vitale S, et al. Relationship between fundus lesion and hematologic parameters at diagnosis. Ophthalmology 1989; 96: 860-4.
17. Abu E-Asrar AM, Al-Momen AK, Kangave D, Harakati MS, Ajarim DS. Correlation of fundus lesion and hematologic findings in leukemic retinopathy. Eur J Ophthalmol 1996; 6: 167-72.
18. Karesh JW, Goldman EJ, Reck K, Kelman SE, Lee EJ, Schiffer CA. A prospective ophthalmic evaluation of patients with acute myeloid leukemia: Correlation of ocular and hematologic findings. J Clin Oncol 1989; 7: 1528-32.