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Ocular Granulocytic Sarcoma: A Case Report and Literature Review of Ocular Extramedullary Acute Myeloid Leukemia

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Introduction

Ocular granulocytic sarcoma (OGS) is a rare complication of acute myeloid leukemia (AML).¹ Postmortem, the choroid is most commonly affected, with conjunctival involvement in only 2% to 4% of cases.² Only 1 case series, few adult OGS cases, and several pediatric cases have been reported.^{2,3} Herein, we describe a subconjunctival relapse of acute myelomonocytic leukemia (AML-M4) and review the literature.

Case Report

A 67-year-old woman presented with fatigue, gingival hyperplasia, and leukocytosis (white blood cell count 115,000/ μ L). Bone marrow (BM) examination revealed AML-M4 with a diploid karyotype. With induction chemotherapy (idarubicin and cytarabine), a complete remission (CR) in the marrow was attained and 3 courses of intermediate-dose cytarabine were administered.

Left conjunctival erythema, with clear secretions, developed 7.5 months into remission. Despite topical antibiotics, symptoms progressed. Magnetic resonance imaging (MRI) revealed soft tissue enhancement of the anterior left orbit without brain abnormalities. Conjunctival biopsy results confirmed relapsed AML-M4.

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Disclosure

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Despite no neurologic deficits, cerebrospinal fluid (CSF) revealed central nervous system (CNS) leukemia. A BM aspirate revealed trisomy 8, with 0.5% leukemic blasts seen on flow cytometry.

After 1 month of weekly intrathecal (IT) liposomal cytarabine and hydrocortisone administration, the CSF cleared. Continuing with maintenance IT liposomal cytarabine, the patient received salvage chemotherapy with mitoxantrone and etoposide (ME) for 5 days, yielding clinical and radiographic resolution of conjunctival findings. A month later, the BM was hypocellular with no flow cytometric evidence of AML, but trisomy 8 persisted. A month later, repeated BM aspiration demonstrated persistent hypocellularity with 4.2% blasts on flow cytometry. At this point, bilateral conjunctival recurrence developed. Because stem cell donors were not found, she was referred to our institution.

At initial consultation (3 months after treatment with ME), bilateral conjunctival erythema and swelling were noted and were worse on the left side (Figure 1A and C). Orbital MRI revealed conjunctival enhancement bilaterally (Figure 1B). BM aspiration examination showed progressive AML-M4, 33% blasts, and trisomy 8. Molecular studies revealed mutant *RAS*, *IDH2*, and *NPM1*. Two days into salvage chemotherapy with clofarabine, idarubicin, and cytarabine, ocular secretions decreased and conjunctival swelling/erythema regressed (Figure 1D). Examination of BM aspiration on day 28 confirmed complete remission (CR). With persistent myelosuppression, the second course of treatment was delayed 66 days, and on day 29 of the second course of treatment, a BM aspirate contained 9% blasts. Conjunctival erythema/secretions gradually developed, but there was no vision loss. With a persistent *RAS* mutation, she was given an MEK inhibitor (GSK1120212, phase 1/2 protocol).

Discussion and Literature Review

Although our patient had nonspecific ocular symptoms, other patients occasionally present with proptosis, pain, chemosis, extraocular motion impairment, visual acuity defects,⁴ and exophthalmos.⁵

In the largest case series to date, ocular manifestations in 53 patients with de novo AML were prospectively evaluated. None had evidence of CNS leukemia. Retinopathy, present in 53%, was associated with significantly lower platelet counts than was seen in patients without retinopathy ($P < .05$). The only symptoms were visual acuity changes in 10 patients; 3 patients with conjunctival involvement had monocytic leukemia (M-4 or M-5), the only finding linked to specific French-American-British (FAB) subtypes. Other findings included conjunctival hemorrhages and retinovascular abnormalities. Most patients received daunorubicin and cytarabine. Ocular findings resolved among induction chemotherapy survivors.⁶

Among OGS case reports, the course of disease varies. OGS occurs at any point during the course of AML, even in the context of a CR. Diffuse ocular infiltration is more common than tumor formation.² OGS can occur without other AML symptoms, preceding marrow

involvement by years.⁵ Other case reports of OGS are summarized in Table 1 and described further on.

OGS can be the initial AML manifestation without other symptoms.² For example, a 73-year-old woman with a myeloproliferative syndrome presented with bilateral ocular chemosis and motion impairment. Conjunctival and marrow biopsy results confirmed OGS and AML. Orbitally directed external beam radiation (30 Gy) was delivered, yielding resolution of lesions and symptoms; however, systemic leukemia ensued. Low-dose cytarabine was initiated with partial response, and the patient died of pneumonia 5 months later with no evidence of OGS.²

Isolated ocular relapse has been described.¹ For example, OGS was found in a 75-year-old woman during hematologic remission. When initially diagnosed with AML-M5 she had an indolent 5-month course before requiring systemic therapy. After commencing low-dose cytarabine treatment (2 weeks), she achieved a hematologic remission that was sustained for 6 months before diffuse scleral/conjunctival monocytic right OGS developed. Ocular relapse occurred while the patient was still in hematologic remission. She was successfully treated with external beam radiation (20 Gy). Unfortunately, 4 months later systemic progression occurred. Despite oral etoposide administration, remission was not achieved. Autopsy confirmed CNS disease without ocular disease.⁷

Similarly, a 47-year-old woman with a history of AML-M4 presented 4 months into remission with a painful left subconjunctival mass. Biopsy results revealed OGS without marrow recurrence. Systemic chemotherapy alone was administered, resulting in rapid resolution. Unfortunately, 3 months later she died of sepsis with chemotherapy-refractory marrow-relapsed AML.⁸ The literature suggests that conjunctival leukemic infiltration responds well to chemotherapy and perhaps does not require external beam radiation.⁹ Our patient's subconjunctival OGS and the patient in this reported case had similar rapid responses to chemotherapy. Although our patient's subconjunctival involvement recurred during her course, salvage treatment again resulted in resolution.

OGS may develop years after remission. A 65-year-old man with a history of AML with maturation (AML-M2) experienced isolated right conjunctival OGS 2 years after CR with ME. Only patchy residual leukemic marrow infiltrate was present at diagnosis of OGS. Ocular external beam radiation yielded long-term resolution.¹⁰

Long intervals are reported between OGS diagnosis and marrow AML development. A 56-year-old man, with right ocular proptosis and blindness underwent computed tomography of the brain, which revealed a large right orbital tumor. Without marrow involvement, non-Hodgkin lymphoma was suspected. After achieving partial remission with 7 courses of CHOP (cyclophosphamide doxorubicin, vincristine, and prednisolone), 40 Gy of radiation were delivered to the right orbit and surrounding areas. During radiotherapy radicular pain developed. L5 compression was noted on a myelogram. CSF sampling revealed AML. After failing IT methotrexate, IT cytarabine was administered, with disappearance of malignant cells. Two years after initial diagnosis, nasopharyngeal and marrow relapse occurred (AML-

M2). Before dying weeks later, his original retroorbital tumor was subsequently confirmed as OGS by immunohistochemical analysis.⁵

Similarly, another patient with large orbital OGS was described. Local external beam radiotherapy concurrent with chemotherapy resulted in complete resolution. The patient was a 71-year-old woman with AML initially treated with doxorubicin and cytarabine. She maintained remission for 1 year before orbital and concurrent systemic relapse. With systemic vincristine, mitoxantrone, and orbital external beam radiation (36 Gy), vision stabilized and proptosis resolved.⁴

These previous cases suggest that treatment of larger orbital lesions may rely on both systemic chemotherapy and external beam radiation (sequential or concurrent) up to 40 Gy. The other cases suggest that nonbulky or diffuse lesions may be successfully treated with 20 Gy for unilateral involvement and 30 Gy for bilateral disease.²

Given the rarity of OGS, no standard guidelines exist regarding radiation dosages or specific chemotherapy regimens. Among the 5 previously mentioned patients receiving external beam radiation, all had somewhat favorable ocular outcomes (although not necessarily favorable overall systemic outcomes).^{2,4,5,7,10}

Compared with other FAB subclassifications, AML-M2, AML-M4, and AML-M5 are more often associated with OGS.^{2,3,6} Extramedullary granulocytic sarcoma (GS) is associated with core-binding factor AML, such as inv(16) and t(8;21). The most commonly reported cytogenetic abnormality associated with GS, t(8;21), has been associated with pediatric OGS.¹¹ To our knowledge, our patient represents the first OGS case with trisomy 8, which has been associated with GS.¹¹

In a pediatric case series of 18 patients with AML and t(8;21),³ 8 presented with GS, among whom 5 had OGS. All were treated with intense systemic and IT chemotherapy. Among OGS patients, 1 with proptosis received local external beam radiation (9 Gy) with improvement before chemotherapy; in the rest, OGS resolved with chemotherapy alone.

Known to penetrate ocular tissue, treatment with high-dose cytarabine for OGS is a reasonable option.^{1,12} In a case report of ocular lymphoma treated with high-dose cytarabine that confirmed therapeutic intraocular concentrations, complete remission was documented.¹²

The only reported patient with OGS treated with topical chemotherapy was a 40-year-old woman with AML-M4 with CNS recurrence. She was undergoing treatment with systemic cytarabine, 6-thioguanine, and daunorubicin, as well as IT cytarabine and methotrexate. After 8 months of therapy, she had attained a partial remission, but experienced a foreign body sensation and blurred vision in her left eye. Examination revealed reduced visual acuity, corneal edema, elevated intraocular pressure, and hypopyon. Biopsy results confirmed OGS. She received intraocular injections of preservative-free methotrexate (15 mg/0.5 mL). Topical betamethasone was also administered 4 times daily. One week later the hypopyon had nearly resolved, the cornea had cleared, and intraocular pressure had decreased. Intraocular methotrexate was continued at 2-week intervals over the next month,

yielding improved vision. Maintenance topical steroids were continued. Two months later systemic and ocular progression ensued. Along with systemic chemotherapy, subconjunctival methotrexate (12.5 mg/0.5 mL), and cytarabine (50 mg/0.5 mL) were administered with hourly topical betamethasone. The subconjunctival chemotherapy was repeated weekly over the next 2 weeks, with marked ocular improvement until the patient's death from systemic leukemia.¹³

Conclusion

OGS may occur at any point in AML—as an initial symptom, during relapse, or even during CR. Conjunctival OGS is so rare that the true incidence is unknown. Both systemic chemotherapy and external beam radiation have yielded successful results. Systemic chemotherapy alone has the potential to alleviate conjunctival involvement without requiring external beam radiation. With nonspecific clinical presentations, pathologic diagnosis is important. OGS notably can occur without the presence of CNS involvement. Further retrospective and prospective studies are warranted to better characterize the incidence and outcomes of OGS.

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Clinical Practice Points

- Ocular granulocytic sarcoma (OGS) can occur at any point in the disease course of acute myeloid leukemia (AML)—as an initial presenting symptom, during systemic relapse, or even in the setting of a complete remission (CR).
- With nonspecific clinical presentations, pathologic diagnosis of OGS is important.
- OGS can occur without central nervous system (CNS) involvement.
- Treatment with systemic chemotherapy alone may alleviate conjunctival involvement without requiring ocular-directed radiotherapy.
- AML-M2 (acute myeloblastic leukemia with maturation), AML-M4 (acute myelomonocytic leukemia), and AML-M5 (acute monocytic leukemia) are more often associated with OGS.
- The most commonly reported cytogenetic abnormality associated with extramedullary AML—t(8;21)—has also been associated with pediatric OGS.

Figure 1.

(A) At Initial Consultation (3 Months After Treatment With Mitoxantrone and Etoposide [ME]), Bilateral Conjunctival Erythema and Swelling Were Noted. (B) Orbital MRI Revealed Conjunctival Enhancement Bilaterally. (C) Conjunctival Erythema and Swelling Were Worse on the Left Side at Initial Consultation. (D) Two Days into Salvage Chemotherapy Ocular Secretions Decreased and Conjunctival Swelling/Erythema Regressed

Table 1

Summary of Case Reports of Ocular Granulocytic Sarcoma

Author (Year)	Sex	Age (y)	Ocular Manifestations	Leukemia Status at OGS Diagnosis	Treatment After Diagnosis of OGS	Overall Outcome
Fleckenstein et al ¹² (2003)	Female	73	Bilateral ocular chemosis and conjunctival involvement	AML transformed from myeloproliferative neoplasm	XRT followed by low-dose cytarabine	Death 5 mo later
Murray et al ⁷ (1984)	Female	75	Unilateral scleral and conjunctival monocytic OGS	AML-M5 in hematologic remission at OGS diagnosis	Ocular-directed XRT	Systemic progression 4 mo later; remission was not achieved despite oral etoposide
Kiradi et al ⁸ (2009)	Female	47	Unilateral subconjunctival OGS	AML-M4 in BM remission at OGS diagnosis	Systemic chemotherapy alone (regimen not specified)	Rapid resolution of ocular manifestations; 3 mo later died of sepsis with refractory marrow-relapsed AML
Hon et al ¹⁰ (2002)	Male	65	Unilateral conjunctival OGS	AML-M2 in remission for 2 y before OGS with patchy BM involvement manifested	Ocular-directed XRT	Long-term ocular resolution
Van Veen et al ⁵ (1991)	Male	56	Large unilateral orbital tumor	Initially no BM involvement at initial OGS diagnosis; relapsed with AML-M2 in BM 2 y after initial ocular presentation	CHOP chemotherapy followed by ocular-directed XRT	CSF later revealed AML; IT methotrexate initiated followed by IT cytarabine; 2 years after initial ocular presentation, nasopharyngeal and marrow relapse occurred; patient died a few weeks later
Watkins et al ⁴ (1997)	Female	71	Large unilateral orbital	AML in remission for 1 y before OGS concurrent with systemic relapse	Systemic vincristine, mitoxantrone, and ocular-directed XRT	Vision stabilized and proptosis resolved
Rootman et al ¹³ (1985)	Female	40	Foreign-body sensation, corneal edema, hypopyon	OGS developed during therapy for active AML-M4 with CNS recurrence	Intraocular methotrexate, topical betamethasone, subconjunctival cytarabine, systemic chemotherapy	Ocular improvement before systemic relapse and death

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CHOP = cyclophosphamide doxorubicin, vincristine, and prednisolone; CNS = central nervous system; CSF = cerebrospinal fluid; IT = intrathecal; OGS = ocular granulocytic sarcoma; XRT = radiotherapy with external beam irradiation.