

CASE REPORT

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Early-stage corneal toxicity secondary to high-dose systemic cytarabine: a case report

Tsuyoshi Mito^{*} , Shun Takeda, Hisanori Miyashita and Hiroshi Sasaki

Abstract

Background High-dose systemic cytarabine chemotherapy may cause fine corneal opacities and refractile microcysts, which are densely distributed in the center of the cornea. Most previous case reports on microcysts have been those following complaints of subjective symptoms, and the findings at the initial stage of development and time-course changes are still unknown. This report aims to clarify the time-course changes of microcysts using slit-lamp photomicrographs.

Case presentation A 35-year-old woman who was treated with high-dose systemic cytarabine therapy (3 courses of 2 g/m² every 12 h for 5 days) for acute myeloid leukemia and presented with subjective symptoms, such as bilateral conjunctival injection, photophobia, and blurred vision, on the 7th day of treatment in both the first two courses. Anterior segment findings by slit-lamp microscopy revealed microcysts densely distributed in the central region of the corneal epithelium. In both courses, microcysts disappeared within 2–3 weeks upon prophylactic steroid instillation. In the 3rd course, daily ophthalmic examinations were conducted from the start of the treatment, and on the 5th day without subjective symptoms, the microcysts in the corneal epithelium appeared evenly and sparsely distributed throughout the cornea except for the corneal limbus. Thereafter, the microcysts accumulated towards the center of the cornea and disappeared gradually. The change from low-dose to full-strength steroid instillation immediately following the occurrence of microcysts in the 3rd course resulted in the peak finding being the mildest compared to that in the past two courses.

Conclusions Our case report revealed that microcysts appeared scattered throughout the cornea before the appearance of subjective symptoms and then accumulated in the center and disappeared. A detailed examination is necessary to detect early changes in microcyst development resulting in prompt and appropriate treatment.

Keywords Cytarabine, Corneal toxicity, Corneal epithelial microcysts, Leukemia, Case report

Background

Cytarabine, an antimetabolite malignant tumor drug, is an essential drug for the treatment of hematopoietic tumors, such as acute myeloid leukemia. High-dose systemic cytarabine chemotherapy is several tens of times higher than the usual dose; thus, it may cause systemic

side effects, such as central nervous system toxicity and myelosuppression [1]. Considering the ophthalmic side effects, it was reported that 85% of the patients reported eye problems, such as conjunctivitis, conjunctival injection, lacrimation, and photophobia [2]. In addition, fine corneal opacities and refractile microcysts, which are densely distributed in the center of the cornea and are reported as a characteristic ocular finding in the corneal epithelium, are likely to occur based on the dose or duration of cytarabine administration [3, 4]. However, most previous case reports on microcysts have been those following complaints of subjective symptoms, and

*Correspondence:

Tsuyoshi Mito
mito@kanazawa-med.ac.jp
Department of Ophthalmology, Kanazawa Medical University, 1-1
Daigaku, Uchinada, Kahoku Ishikawa 920-0293, Japan



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the findings at the initial stage of development are still unknown. Moreover, there have been only a few reports detailing time-course changes, since ocular symptoms coincide with the systemic side effects attributed to high-dose cytarabine therapy, and it is often difficult to perform an ophthalmic examination in such situations.

We report the initial onset of microcysts in the corneal epithelium before subjective symptoms and their subsequent course using slit-lamp photomicrographs.

Case presentation

A 35-year-old Japanese woman was diagnosed with acute myeloid leukemia and was treated with a combination of idarubicin and cytarabine as remission induction therapy. High-dose systemic cytarabine therapy was subsequently scheduled for 3 courses, every 2 months, as consolidation therapy. A single course comprised cytarabine administration at 2 g/m^2 10 times every 12 h for 5 days. From the morning of the 7th day following the start of the first course, she presented with eye pain, lacrimation, photophobia, and blurred vision in the left eye, and was referred to our department of ophthalmology the next day. At the first examination, her corrected visual acuity (VA) was 20/25 in the right eye and 20/40 in the left eye. Considering the anterior segment findings, the slit-lamp microscopy revealed bilateral mild conjunctival hyperemia, mild superficial punctate keratopathy, and granular microcysts densely distributed in the central region of the corneal epithelium, which were slightly more in the left eye (Fig. 1). There was no inflammation in the anterior chamber, no abnormalities upon corneal endothelium examination, no abnormal findings in the cornea upon anterior segment optical coherence tomography (CASIA2; Tomey Corporation, Nagoya, Japan), and no obvious abnormalities were detected in the optic media and fundus.

To prevent corneal epithelial damage attributed to cytarabine, the patient was administered 0.02% fluorometholone eye drops and artificial tears four times a day by the oncologist at the same time as the start of instillation treatment; however, after the ophthalmology referral, 0.1% fluorometholone eye drops and artificial tears were administered 6 times a day, and ofloxacin eye ointment was applied once before sleep. On the 11th day following the start of the treatment, the patient was isolated in a sterile room owing to cytopenia following severe myelosuppression, which is a side effect of high-dose systemic cytarabine therapy; therefore, we conducted a bedside examination. Thereafter, the microcyst gradually decreased, subjective symptoms disappeared on the 14th day, the microcyst disappeared completely on the 28th day, and the corrected VA finally recovered to 20/20 in both eyes.

At the start of the second course, 0.1% fluorometholone eye drops and artificial tears were prophylactically administered four times a day; however, she reported eye pain, lacrimation, and blurred vision 7 days following the start of treatment, similar to the first course. She underwent reexamination at our department, and densely distributed microcysts in the center of the cornea, were detected in both eyes. The 0.1% fluorometholone instillation was increased to 6 times a day, and the subjective symptoms improved on the 9th day; the microcysts disappeared on the 17th day.

A high possibility of the microcyst recurrence with the start of the third course was considered, and the patient underwent daily ophthalmic examinations from the start date of the treatment. No abnormal findings were detected in the cornea until the 4th day; however, on the morning of the 5th day, the fluorescein-negative microcysts, which were evenly and sparsely distributed over the entire cornea except for the width of approximately

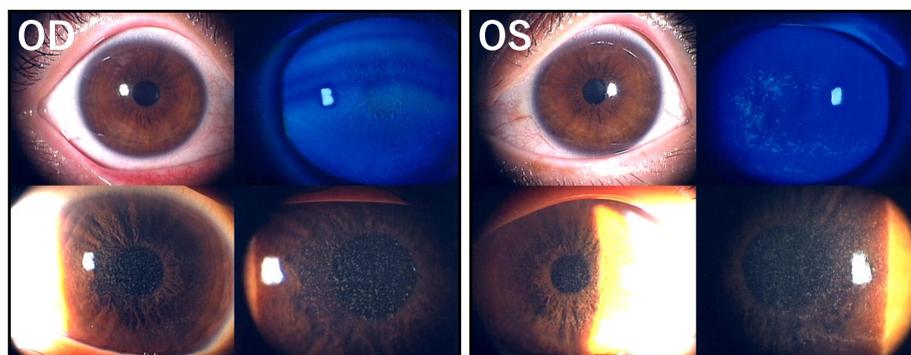


Fig. 1 Slit-lamp photomicrographs of microcysts caused by high-dose systemic cytarabine therapy in the 1st course. On the 8th day after the start of cytarabine therapy, bilateral mild conjunctival hyperemia, ciliary injection, and superficial punctate keratopathy were observed. The transillumination images showed fine corneal opacities and refractile microcysts densely distributed in the center of the corneal epithelium; however, no inflammation in the anterior chamber was observed. OD, right eye; OS, left eye

1–2 mm in the corneal limbus, were observed without subjective symptoms (Fig. 2). Considering the findings of recurrence, 0.1% fluorometholone instillation, which was administered prophylactically, was changed to 0.1% beta-methasone instillation six times a day. On the 6th day, the microcysts accumulated slightly below the center of the cornea, and on the 7th day, the accumulation of microcysts in the center of the cornea peaked; however, the peripheral area of the cornea became transparent and no new microcysts were observed. Similar to the previous two courses, subjective symptoms appeared on the 7th day following the start of treatment; however, they were milder than those at the time of the previous two courses. On the 8th day, the microcysts in the center of the cornea slightly disappeared and only remained in a linear shape (Fig. 3a–j). Thereafter, since the patient was isolated in a sterile room owing to cytopenia, it was impossible to record the corneal lesions by taking photographs. Approximately 1 week later, the microcysts completely disappeared, and the final corrected VA was 20/20 in both eyes; no ophthalmologic residual disorders were observed.

Discussion and conclusions

To our knowledge, this is the first case to record corneal lesions on slit-lamp photomicrographs depicting the initial onset and time courses of the microcysts induced by high-dose systemic cytarabine therapy in patients with acute myeloid leukemia. Corneal toxicity owing to high-dose systemic cytarabine therapy generally appears on the 5th to 7th day following the start of treatment and then spontaneously disappears in nearly a week following the appearance [3]. Since the onset of corneal toxicity coincides with the worsening of leukemia or systemic side effects, such as severe myelosuppression, performing frequent ophthalmic examinations is challenging and often requires bedside visits. Therefore, there has been no detailed report on the course of microcysts. Previous reports have demonstrated that microcysts were densely

distributed in the central region of the cornea [3, 4] however, our daily observations revealed that microcysts had already occurred 1–2 days prior to the development of subjective symptoms, and in the early stages of the disease, microcysts were evenly and sparsely distributed throughout the cornea except for the corneal limbus, and thereafter, they accumulated in the center of the cornea and disappeared gradually.

Corneal toxicity attributed to cytarabine was first recognized in the 1960s; cytarabine ophthalmic preparation, which was a candidate therapeutic agent for herpes keratitis, reportedly caused drug toxicity to the corneal epithelium *in vivo* [5, 6]. In 1981, Hopen et al. reported a case of corneal toxicity in high-dose systemic cytarabine therapy for patients with leukemia and referred to the granular lesion in the corneal epithelium as a “microcyst [3].” In their reports, pathological findings revealed that the degenerated cells, which are a mixture of pyknosis and cytoplasmic fragments, were the main body of the microcyst, and not cystic cavities. The following hypothesis is proposed to explain the occurrence of microcysts in the corneal epithelium. Generally, in the corneal epithelial layer, transient amplifying cells (TACs) differentiate from limbal epithelial stem cells (LESCs) in the corneal limbus and migrate towards the corneal center, undergo intermittent cell division, differentiate into superficial cells, and eventually fall off from the surface layer, thereby maintaining the homeostasis of the corneal epithelium [7]. On the other hand, cytarabine is metabolized to Ara-CTP in the cytoplasm and inhibits DNA polymerase, DNA repair, and RNA synthesis. Since these actions prominently occur in the cells in the S phase (DNA replication phase) of the cell cycle, cells with faster dividing cycles are more likely to be affected [8]. Thus, cytarabine may affect TACs with a short cell cycle compared to LESCs with a long cell cycle in the corneal epithelium [9]. If the LESCs are more susceptible

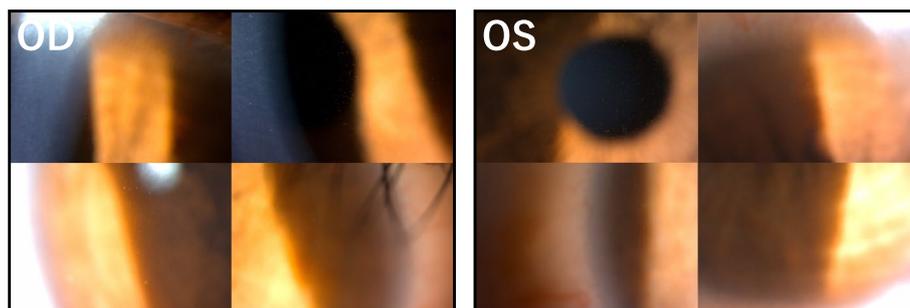


Fig. 2 Slit-lamp photomicrographs immediately after the occurrence of microcysts in the 3rd course. On the 5th day after the start of cytarabine therapy, bilateral microcysts were evenly and sparsely distributed throughout the cornea except for the corneal limbus. No subjective symptoms were observed at this time. OD, right eye; OS, left eye

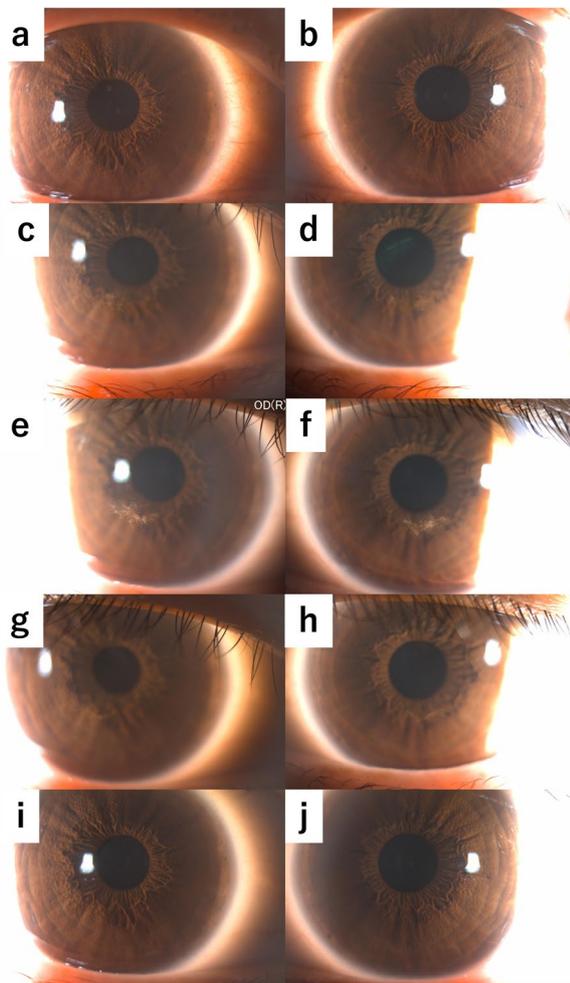


Fig. 3 Time-course changes of microcysts in the 3rd course. a, c, e, g, i, right eye; b, d, f, h, j, left eye. On the 5th day (a, b) of the start of cytarabine therapy, eye drops were changed from 0.1% fluorometholone to 0.1% betamethasone immediately following the onset of microcysts. On the 6th day (c, d), the microcysts began to accumulate slightly below the center of the cornea. On the 7th day (e, f), microcyst accumulation in the center of the cornea was at the peak. There were no microcysts in the corneal limbus. The patient complained of subjective symptoms at this time. On the 8th day (g, h), the microcysts began to disappear gradually. It was impossible to record the corneal lesions as photomicrographs from the next day since the patient was isolated in a sterile room owing to the cytopenia. On the 21st day (i, j), microcysts completely disappeared and no ophthalmologic residual disorders were observed

to cytarabine, early-stage microcysts are expected to develop at high density from the corneal limbus; however, in this case, the microcysts were evenly and sparsely distributed throughout the cornea with transparency of the corneal limbus, supporting the hypothesis that the TACs that are widely present in the corneal epithelium are damaged by cytarabine.

Guthoff et al. observed the time-course changes of cells damaged by cytarabine in the center of the cornea using

in vivo confocal microscopy following subjective symptoms [10]; they observed degenerated cells in the basal epithelial layer on the 1st day, in the basal–apical layer on the 3rd to 4th days, and many degenerated cells in the superficial layer on the 9th to 14th days. These findings suggest that degenerated cells move from the deep layer to the surface layer of the corneal epithelium. In this observation as well, the time-course change of the microcysts scattered throughout the cornea, accumulating at the center of the cornea and disappearing gradually, may be one of the important findings for clarifying the processes from the development of microcysts to their disappearance. Microcysts densely distributed in the central region of the cornea, as described in previous papers, are thought to be the result of degenerated cells after accumulating towards the center for several days owing to inhibited cell synthesis in the corneal epithelial basal cell layer.

The effectiveness of steroid eye drops (1% prednisolone) for corneal toxicity by cytarabine has been previously reported [11, 12]. The suppression of DNA replication by steroids would render corneal epithelial basal cells less susceptible to the effects of cytarabine. Thus, steroids were administered prophylactically in all three courses; however, microcysts at the peak were most severe in the 1st course owing to the administration of the weakest 0.02% fluorometholone instillation. In the 3rd course, the same 0.1% fluorometholone instillation as in the 2nd course was administered prophylactically; however, owing to changing the eye drops to 0.1% betamethasone instillation immediately following the onset of fine microcysts before the development of subjective symptoms, the degree of microcysts at the peak was the mildest and the subjective symptoms were minor. This change would have prevented the injury of the TACs, associated with the remaining course of cytarabine administration over the next few days. Thus, although steroids cannot completely prevent corneal toxicity attributed to cytarabine, it may be possible to suppress the peak of symptoms by increasing the strength of the eye drops and the instillation times.

This case report presents findings from the pre-occurrence to the disappearance of microcysts attributed to high-dose systemic cytarabine therapy. A detailed examination of patients receiving cytarabine therapy without subjective symptoms is necessary to detect early changes in microcyst development resulting in prompt and appropriate treatment, thereby enabling the reduction of corneal toxicity and its concomitant subjective symptoms.

Abbreviations

LESCs	Limbal epithelial stem cells
TACs	Transient amplifying cells
VA	Visual acuity

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Authors' contributions

TM conducted the report plan, and drafted this manuscript. ST and HM contributed to data acquisition. HS supervised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

No ethical approval required. This case report was performed in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent for the publication was obtained from the patient of this case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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References

1. Stentoft J. The toxicity of cytarabine. *Drug Saf.* 1990;5:7–27.
2. Herzig RH, Wolff SN, Lazarus HM, et al. High-dose cytosine arabinoside therapy for refractory leukemia. *Blood.* 1983;62:361–9.
3. Hopen G, Mondino BJ, Johnson BL, et al. Corneal toxicity with systemic cytarabine. *Am J Ophthalmol.* 1981;91:500–4.
4. Ritch PS, Hansen RM, Heuer DK. Ocular toxicity from high-dose cytosine arabinoside. *Cancer.* 1983;51:430–2.
5. Kaufman HE, Capella JA, Maloney ED, et al. Corneal Toxicity of Cytosine Arabinoside. *Arch Ophthalmol.* 1964;72:535–40.
6. Elliott GA, Schut AL. Studies with cytarabine HCl (CA) in normal eyes of man, monkey and rabbit. *Am J Ophthalmol.* 1965;60:1074–82.
7. Dora NJ, Hill RE, Collinson JM, et al. Lineage tracing in the adult mouse corneal epithelium supports the limbal epithelial stem cell hypothesis with intermittent periods of stem cell quiescence. *Stem Cell Res.* 2015;15:665–77.
8. Mompalmer RL. A model for the chemotherapy of acute leukemia with 1-beta-D-arabinofuranosylcytosine. *Can Res.* 1974;34:1775–87.
9. Lochhead J, Salmon JF, Bron AJ. Cytarabine induced corneal toxicity. *Eye (Lond).* 2003;17:677–8.
10. Guthoff T, Tietze B, Meinhardt B, et al. Cytosine-arabioside-induced keratopathy: a model of corneal proliferation kinetics. *Ophthalmol.* 2010;224:308–11.
11. Lass JH, Lazarus HM, Reed MD, et al. Topical corticosteroid therapy for corneal toxicity from systemically administered cytarabine. *Am J Ophthalmol.* 1982;94:617–21.
12. Lazarus HM, Hartnett ME, Reed MD, et al. Comparison of the prophylactic effects of 2-deoxycytidine and prednisolone for high-dose intravenous cytarabine-induced keratitis. *Am J Ophthalmol.* 1987;104:476–80.

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