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Corneal Limbal Stem Cell Deficiency Associated with the Anticancer Drug S-1

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ABSTRACT

Purpose. An oral antineoplastic drug, S-1, is known to be more effective with less toxicity and fewer gastrointestinal side effects than the conventional intravenous 5-fluorouracil. We report a case of limbal stem cell deficiency that occurred in a patient receiving chemotherapy using S-1 alone for gastric cancer.

Case Report. A 65-year-old woman with symptoms of grittiness and epiphora in both eyes for several months was referred to the ophthalmology clinic. She had been receiving S-1 orally after total gastrectomy for advanced gastric cancer. Slit lamp examination revealed an irregular hazy corneal epithelium in both eyes that extended to the center of the cornea overlying the pupil and showed late staining with fluorescein dye. Palisades of Vogt at the superior limbus were absent in both eyes. Best-corrected distance vision was 20/50 in both eyes with all other structures of the anterior and posterior segment unremarkable including a patent lacrimal drainage system. There was no change in the corneal lesions of either eye despite 3 months of topical therapy. The lesions did resolve in 4 months after discontinuation of S-1 therapy owing to acute renal failure.

Conclusions. Early detection of this adverse reaction before significant visual loss through regular follow-up appears to be important in patients receiving S-1 therapy.

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Key Words: adverse effect, cornea, limbal stem cell deficiency, S-1, 5-FU

S-1, an oral pyrimidine-based antimetabolite, is a recently developed cancer chemotherapeutic drug. It is composed of tegafur, which is a prodrug of 5-fluorouracil (5-FU), and two biochemical modulators, 5-chloro-2,4-dihydroxy-pyridine and potassium oxonate.[1] This novel drug is known to be more effective with less toxicity and fewer gastrointestinal side effects than the conventional intravenous 5-FU. Therefore, it is the most widely used drug for gastric cancer, and the indications for the use of this drug in other solid tumors have also widened.[2,3]

Ocular adverse effects of chemotherapy with intravenous 5-FU and oral S-1, such as nasolacrimal drainage obstruction, have been reported.[4,5] Serious corneal complications associated with significant reduction in visual acuity have been scarcely observed. Complete recovery of presumed drug-induced limbal stem cell deficiency (LSCD) after cessation of S-1 has not been described.

We report a patient who had vision-impairing corneal LSCD while receiving adjuvant chemotherapy with S-1 for gastric cancer. This case should raise awareness of this potentially vision-threatening side effect of S-1 along with the importance of comanagement between oncologists and eye care providers.

CASE REPORT

A 65-year-old woman with symptoms of grittiness and epiphora in both eyes for several months was referred to the ophthalmology clinic by the oncologist for the evaluation of lacrimal drainage. Her medical history revealed total gastrectomy for advanced gastric cancer 6 months prior followed by adjuvant chemotherapy with S-1 (TS-1; Taiho Pharmaceutical, Japan). No other systemic disease, current medications, or history of trauma was reported. At her initial visit, she had completed three cycles of chemotherapy consisting of 80 mg of S-1 daily for 4 weeks followed by a 2-week interval between treatments. She had received 6860 mg of S-1 in total, because she had taken 100 mg of S-1 daily for the first week during the first cycle, which was reduced to 80 mg for the succeeding week because of stomatitis.

Uncorrected distance visual acuity was 20/100 in the right eye and 20/125 in the left. Best-corrected distance visual acuity (CDVA) was 20/50 in both eyes with refractions of +3.25 −3.75 × 085

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for the right and +2.00 −0.75 × 090 for the left. Keratometry revealed corneal astigmatism of 3.0 diopters (D) in the right eye and 1.0 D in the left eye. The results of tests for tear fluid in the right eye and left eye were as follows: tear breakup time was 3 and 4 seconds, respectively; Schirmer test results were 18 and 16 mm, respectively; tear meniscus height was 0.3 mm in both eyes. Dilation and irrigation of the nasolacrimal drainage pathways did not show a functional blockage in either eye. There was no regurgitation through the opposite punctum with irrigation. Slit lamp examination revealed an irregular hazy corneal epithelium that extended to the center of the cornea involving the visual axis and showed late staining with fluorescein dye (Fig. 1A, B). The Palisades of Vogt (POV) at the superior limbus were absent in both eyes, and there were no other remarkable findings including visually significant cataract. No other possible pathology to explain the decreased CDVA such as maculopathy and corneal edema was found during dilated fundus examination, macular optical coherence tomography, and corneal thickness measurement. A diagnosis of partial LSCD in both eyes was made and was treated with topical antibiotic (moxifloxacin hydrochloride; Vigamox, Alcon, USA) and topical steroid (prednisolone acetate; Pred Forte, Samil-Allergan, Korea). The corneal lesion and symptoms including reduced vision showed no signs of improvement despite 3 months of topical therapy. The patient was then lost to follow-up for 4 months.

After this period, the patient was again referred for a reexamination of her eyes. Her medical history in the meantime revealed that S-1 was discontinued for almost 4 months because of an episode of acute renal failure. She reported that all symptoms disappeared gradually after discontinuation of the drug. Uncorrected distance visual acuity was improved to 20/20 in the right eye and 20/25 in the left eye, and refractive errors were decreased to +1.25 −1.00 × 80 and +0.75 −0.75 × 85, respectively. Corneal astigmatism also decreased to 0.50 D in both eyes, and CDVA was 20/16 in both eyes. The results of tests for tear fluid in the right eye and left eye were improved: tear breakup time was 8 and 9 seconds, respectively; Schirmer test results were 15 and 14 mm, respectively; tear meniscus height was 0.1 mm in both eyes. On slit lamp examination, the corneas had clear and regular surfaces with no fluorescein staining. The previous absent POV at the superior limbus were now visible in both eyes (Fig. 1C, D).

DISCUSSION

Problems with the limbal stem cell population result in a decrease in the ability of the corneal epithelium to repopulate itself.

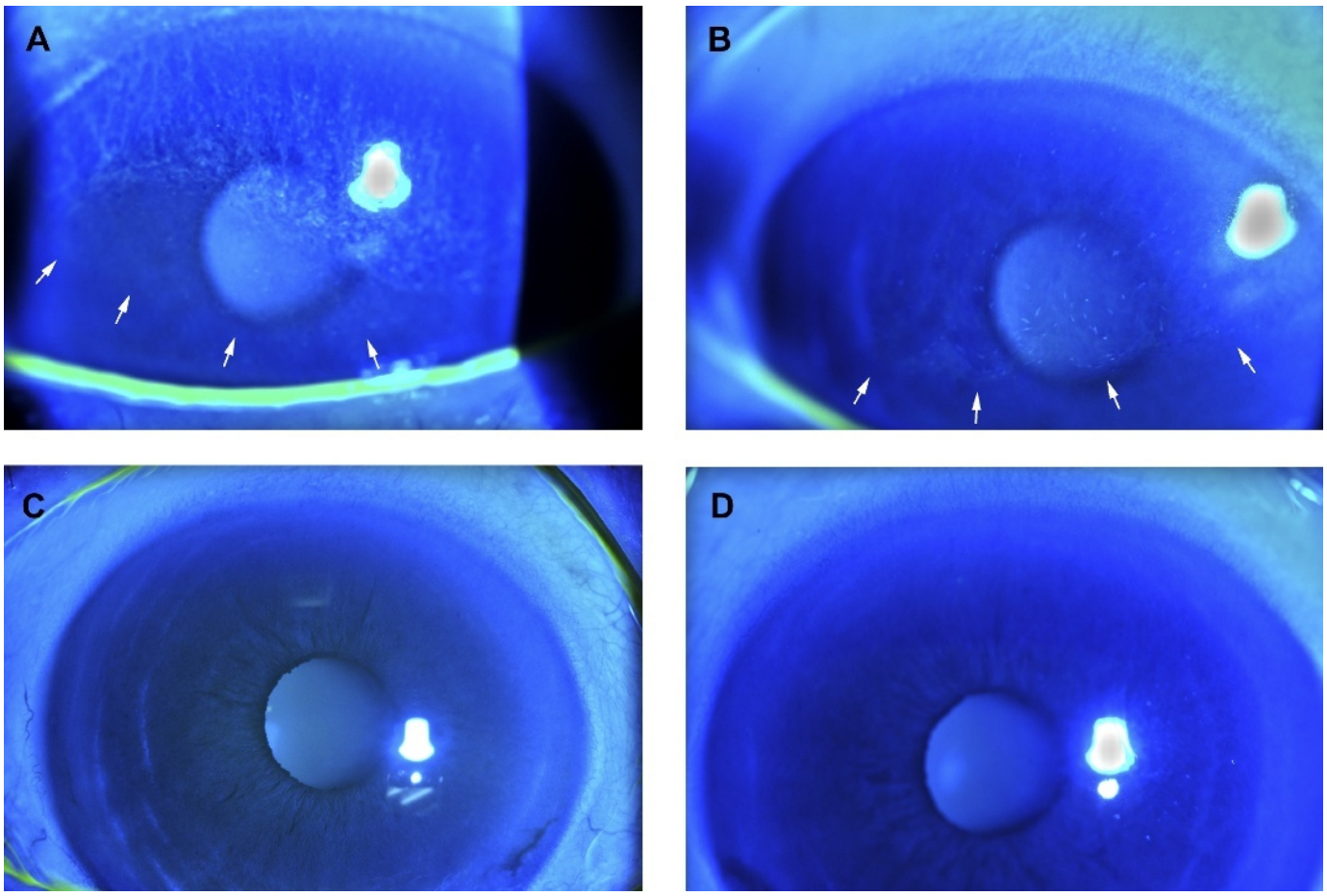

FIGURE 1.

Slit lamp photographs showing an irregular hazy corneal epithelium that extended to the center of the cornea overlying the pupil (arrows) and late staining with fluorescein dye. The POV at the superior limbus were absent in both eyes: (A) right eye; (B) left eye. The epithelial abnormality resolved 4 months after discontinuation of S-1 owing to acute renal failure, and limbal contour at superior quadrant was more obvious because of restoration of POV in both eyes: (C) right eye; (D) left eye.

A state of LSCD can be secondary to a number of etiologies resulting in either a reduction in the total number of limbal stem cells or an abnormality in the ability of the stem cells to function adequately. In these situations, patients often complain of redness, irritation, photophobia, and decreased vision from corneal opacity and irregular astigmatism. Early slit lamp findings include loss of the POV, late staining of the epithelium with fluorescein, corneal neovascularization, and the development of peripheral pannus. Overtime, corneal findings may progress to involve the central cornea. Initially, the epithelium becomes irregular and hazy; however, corneal findings may progress to persistent epithelial defects, stromal scarring, ulceration, and even perforation.[6] Identification of goblet cells on the surface of the cornea is useful in making the diagnosis of LSCD; however, this is not mandatory because goblet cells may be completely absent in some advanced diseases. Conservative treatment, such as intensive use of nonpreserved lubrication and topical corticosteroids, usually provides temporary remission, but the condition tends to deteriorate over time. Therefore, in most cases, surgical options including amniotic membrane graft transplantation and ocular surface reconstruction are required to restore normal corneal structure and function.[7]

5-Fluorouracil is a pyrimidine analog that interferes with nucleic acid synthesis. Its ability to alter DNA and RNA synthesis has led to its widespread use topically not only for the treatment of ocular surface neoplasia but also for the regulation of wound healing after glaucoma, pterygium, and refractive surgeries.[8] Although 5-FU is known to be toxic to normal corneal structures including epithelial cells and keratocytes,[9] only mild side effects such as punctate keratopathy, epithelial defects, and filamentary keratitis have been reported. This relatively mild level of toxicity may be attributed to the low concentrations of 5-FU used for topical ocular applications.[10]

The incorporated biochemical modulators 5-chloro-2,4-dihydroxy-pyridine and potassium oxonate that make up S-1 may result in higher levels of serum 5-FU. This is attributed to their ability to interfere with drug degradation by the liver and its consumption in the intestine after conversion from prodrug form.[1] The concentration of 5-FU in the tear fluid and corneal limbus, which has an abundant vascular network, would be consequently increased proportionally. In addition, the concentration of 5-FU is known to be higher in tissues composed of highly mitotically active cells compared with that in the plasma.[11] Therefore, in the limbus, where the corneal stem cells reside, its concentration could be augmented. Longer durations of chemotherapy treatment could be another factor responsible for increasing cumulative concentrations of 5-FU. Taking all these points into consideration, the concentration of 5-FU could be increased up to a level adequate to induce serious toxicity in the corneal limbus after the administration of S-1. Further studies regarding the concentration of 5-FU in the tissue or tear fluid are necessary to elucidate this hypothesis.

It must be presumed that the inflammation induced by S-1 could augment LSCD after considering the presence of activated keratocytes and loss of subepithelial nerves observed in the S-1–treated patients by using a confocal microscope.[12] This emphasizes the importance of early recognition of the complication presented in this study because activated keratocytes can produce matrix metalloproteinases and induce corneal haze, which potentially threatens vision.[13]

The reported case meets five of the suggested seven criteria to support an adverse drug reaction.[14] Establishing a dose-response relationship and attempting a rechallenge given the drug-induced renal toxicity could not be attempted for ethical reasons. Therefore, LSCD was presumed to have occurred as a serious ocular adverse reaction associated with the anticancer drug S-1. Although nasolacrimal drainage obstruction has been frequently reported after the use of systemic 5-FU including prodrug,[4,5] a serious corneal complication such as LSCD should also be considered a cause of epiphora in a patient receiving S-1 treatment. This case should draw attention to LSCD caused by S-1 treatment and emphasize how early detection and disconsolation of treatment can improve prognosis.

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