Dacryoendoscopic Findings of Patients With Nasolacrimal Obstruction Associated With Cancer Treatment

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Research Article

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Abstract

Purpose

To investigate the etiology of lacrimal drainage obstruction(LDO) of people who underwent systemic chemotherapy(CTx) or radioactive iodine treatment(RAI) by using dacryoendoscopy and at the same time performing microendoscopic silicone tube insertion(MESI) to treat epiphora.

Method

From July 2017 to December 2020, the medical records of 11 patients(16 eyes) who diagnosed LDO after the CTx or RAI and underwent MESI were reviewed retrospectively.

Results

The mean age was 69.0±8.2 years and prevalence of female was higher(2:9). The mean duration of the epiphora was 28.3±35.5 months, and the mean start period of epiphora after treatment was 29.5±36.5 months. In all patients, the tear meniscus height was significantly reduced after surgery. Dacryoendoscopic findings were as follows (n,(%)): mucus, 10(62.5); granulation, 4(25.0); fibrotic membrane, 6(37.5); stenosis, 5(31.3); edema, 4(25.0). Levels of obstruction were as follows (%): canaliculus, 10(62.5); lacrimal sac, 11(68.8); nasolacrimal duct, 5(37.3); inferior turbinate, 4(25.0). There was no difference in level of obstruction, but the granulation finding was significantly often in RAI (p=0.038), while mucosal edema was more often in CTx(p=0.025).

Conclusions

The dacryoendoscope enabled us to observe the nasolacrimal system in real time and examine the lesions causing LDO. Even though CTx or RAI is considered as mandatory treatment for the patients, it could affect their whole body including LDS. However, MESI can be a treatment of choice for LDO after the treatment. It is important to refer the patients suffering from epiphora to ophthalmologists for improving their quality of life by non-invasive treatment during and after additional treatment.

Key Message

- There have been a number of reports of cases where the lacrimal drainage obstruction(LDO) occurred after the systemic chemotherapy(CTx) and radioactive iodine treatment(RAI), but since we didn’t have a direct look inside it, so the exact cause of LDO is unknown.
- In this paper, patients who diagnosed LDO after the systemic CTx or RAI was directly identified the location of the obstructive lesion inside lacrimal drainage system by using dacryoendoscopy, and recanalized the duct followed by silicone tube insertion (MESI, Microendoscopic silicone tube insertion) in order to improve the tearing symptom.

- In dacryoendoscopic findings, the granulation was significantly more often in RAI patients (p=0.038), and the mucosal edema was significantly more often in CTx patients (p=0.025).
- MESI can be a treatment of choice for LDO after the systemic CTx or RAI

Introduction

Many studies have documented that systemic use of chemotherapy (CTx) can cause lacrimal drainage obstruction (LDO) and docetaxel is the most well-known drug causing LDO. 1)-6) According to Constanza et al, S-1 and radioactive iodine have been reported to cause a lacrimal duct failure 7). Yusuke et al reported the results of the higher concentration of docetaxel treatment, the more people complained of tear symptoms 8). There have been a number of reports of cases where the LDO occurred after the systemic CTx and RAI, but since we didn't have a direct look inside it, so the exact cause of LDO is unknown.

The causes of epiphora after the CTx may be explained two suggested routes. The first suggested mechanism involves direct secretion into the tear film 2). CTx agent passes along the lacrimal drainage, causing chronic inflammation and fibrosis of mucosa, resulting in LDO. The second suggested mechanism includes the damage of the lacrimal drainage system secondary to the systemic effects of chemotherapeutic agents 1). I-131 therapy in thyroid cancer also causes an increased incidence of nasolacrimal drainage system obstruction, a relation likely to be dose-related. 11-12) But yet, the direct pathologic cause of this obstruction has not yet been fully understood since we could not examine directly inside LDS before application of dacryoendoscopy in this field.

The dacryoendoscope has the advantage of being able to observe the nasolacrimal duct from the punctum to the Hasner's valve in real time and check the lesions causing LDO. According to Lim et al 9), it enabled them to visualize inside he nasolacrimal duct on site, as well as examine lesions that could not be identified in the dacryocystography(DCG). Currently, the primary surgical treatment for LDO is recanalization or bypass surgery for tear drainage with silicon tube insertion (STI). According to Kim et al 10), it was reported that the LDO caused by S-1 responded well to silicone intubation in 4 cases.

In this study, patients who complained of epiphora due to the LDO associated with combined treatment such as systemic CTx or RAI following cancer surgery were studied. Using dacryoendoscopy, we directly identified the location of the obstructive lesion inside lacrimal drainage system and recanalized the duct followed by silicone tube insertion (MESI, Microendoscopic silicone tube insertion) in order to improve the tearing symptom.

Materials And Methods

This study and data collection protocol were approved by the Institutional Review Board of CHA Bundang Medical Center (CHAMC IRB 2018-01-027), and our study design adhered to the tenets of the Declaration of Helsinki. Informed consent about clinical information and specific consent about publication of

identifying information/images in an online open-access publication were obtained from each subject before enrollment.

From July 2017 to December 2020, the medical records of patients diagnosed with LDO and underwent MESI were reviewed retrospectively at CHA Bundang Medical Center, Seongnam, South Korea. Eleven patients, 16 eyes were diagnosed LDO and treated with dacryoendoscopy after the CTx and RAI. (Table 1) We carried out vision and intraocular pressure test, slit lamp examination, history taking, canaliculus irrigation test. The severity of epiphora was graded using Munk's scale. Tear meniscus height, punctal diameter and punctal reserve were measured by OCT (SPECTRALIS®, Heidelberg Engineering, GmbH, Heidelberg, Germany).

The irrigation test was performed by inserting a 26-gauge needle with a blunt tip into a 2mL syringe filled with normal saline solution, inserted into the punctum, and then injected saline to verify that it was passed over to the nose or throat. According to results, it was classified hard stop/soft stop, and well passed/not passed.

Patient who were strongly suspected of LDO proceeded dacryocystography(DCG). DCG was performed after instilled a drop of proparacaine 0.5% (Alcaine; Alcon, TX, USA) into the conjunctival sac, check whether the contrast agent runs along the lacrimal drainage system by injecting the contrast agent, lohexol (Bonorex®; Central Medical Service, Seoul, South Korea) while scanning x-rays. By DCG, we classified primary; narrowing, obstruction and secondary pattern; beaded, dilation.

By measurement of tear meniscus height, irrigation test and DCG, patients were diagnosed with LDO. Patient who underwent systemic CTx or RAI but who did not know the exact drug were excluded. Also we excluded cases that diagnosed with cancer but performed only surgery. Case that underwent additional ophthalmic surgery such as conjunctivochalasis, conjunctival lesion or caruncle lesion were also excluded.

Surgical treatment was done under general anesthesia or local anesthesia by using dacryoendoscopy and inserting a silicon tube, as we call from now on, MESI (microendoscopic silicone tube insertion). After extending the punctum using the punctum extensor and spring scissor, by inserting the 0.9mm diameter probe tip, bent type dacryoendoscope (RUIDO Fibercope, FiberTech Co., Tokyo, Japan) through the punctum, check the internal conditions of the lacrimal duct system by flowing through saline, leading to the upper and lower canaliculus, lacrimal sac, nasolacrimal duct and inferior turbinate.

Dacryoendoscopic findings were classified according to the location and features of obstruction. The obstructive lesion was pushed out by the sheath guided by the endoscopy and pressure of perfusion solution with a syringe connected with probe, and silicone tube insertion was performed from punctum to nasal cavity and fixed with hemolock. Dacryoendoscopic findings were classified into space-occupying and structural changes. The space-occupying group included mucus, stones, and granulation findings; the structural changes group included fibrotic membrane, stenosis, edematous findings.

Surgeries were deemed successful when the patient's subjective results are satisfied with result, lower tear meniscus height is less than 300μm and the irrigation test was passed after extubation.

Statistical analysis was performed using IBM SPSS software (ver. 26.0; IBM Corp., Armonk, NY, USA). An independent t test and Mann-Whitney test were used to compare parametric and non-parametric groups, respectively. A paired t test was performed to compare before and after surgery data.

Results

There were various types of CTx regimen used in each patient, which included Cyclophosphamide, Methotrexate, 5-Fluorouracil, Docetaxel, carboplatin, herceptin, Perjeta, pemetrexed, paclitaxel, Ifostamide, Etoposide.

The mean age was 63.2±11.8 years and prevalence of female was higher than that of male (2:9). The right eye was similar with 7 (43.8%) and the left eye with 9 (56.3%). The mean duration of the epiphora was 28.3±35.5 months, and the mean onset period of epiphora after CTx or RAI is 29.5±36.5 months. Mean munk scale was 3.8±1.6 and preoperative lower tear meniscus height was 458.1±184.2μm.

Between CTx group and RAI group, most of all values are no statistically significantly difference. But interestingly, patient with CTx group's onset of epiphora(3.0±4.0) was significantly shorter than that of RAI group(52.6±36.5). (p=0.001) (Table 2)

As shown in (Table 3), there was no difference between CTx patients and RAI patients in clinical outcomes of LDO patients. By irrigation test, the ratio of hard stop was three times higher than soft stop. Well passed eyes were 5 (31.3%), and not passed eyes were 11 (68.8%). CTx group's percentage of passage was 75%, and that of RAI group was 62.5%. Mean duration of tube insertion was 5.6±0.6 months. By dacryoendoscopy, 5 eyes (31.3%) had LDO at one levels, 11 patients (68.7%) had LDO at two or more levels simultaneously. There was no difference between two groups in level of obstruction. Levels of obstruction were as follows (%): lacrimal sac, 11(36.6); canaliculus, 10(33.3); nasolacrimal duct, 5(16.6); inferior turbinate, 4(13.3). (Figure 1) The success rate was 100% in both patients receiving CTx, or RAI group. Dacryoendoscopic findings were as follows (%): mucus, 10(35.7); granulation, 4(14.2); fibrotic membrane, 5(17.8); stenosis, 5(17.8); edema, 4(14.2). (Figure 1) In dacryoendoscopic findings, the granulation was significantly more often in RAI patients (p=0.038), and the mucosal edema was significantly more often in CTx patients (p=0.025) (Table 3)

(Table 4) is about the lacrimal flow test outcome categorized by obstruction level. Based on lacrimal sac, canaliculus and lacrimal sac are divided into pre-sac and sac, nasolacrimal duct, and inferior turbinate are divided tnto post-sac. According to the results of irrigation test, all 3 eyes were not passed in the case of Post-sac. The primary pattern(narrowing, obstruction) of DCG was more common than that of secondary pattern(beaded, dilation). The results of the dacryoendoscope showed more structural changes than those of the secretory findings. The success rate was 100% for each part.

Conclusions

In this study, we reviewed the chart of patients who previously diagnosed LDO after systemic CTx or RAI and complaining the epiphora and preceded MESI. In demographics about before surgery, there was no significant difference between the two groups.

There was no significant difference between two groups but CTx group's onset of epiphora is significantly earlier than RAI group. Mean onset time after CTx was 3.0 month, which is sililar to 1.4~6 month as Park et al reported. 13) In CTx group, the most obstructed area was canaliculus, 6 (75.0) and lacrimal sac, 6 (75.0). Bartley et al. classified secondary acquired lacrimal drainage obstruction by infectious, inflammatory, neoplastic, traumatic, or mechanical causes. 14) NLDO after CTx might be systemic inflammatory cause, and epiphora occurs immediately after CTx is also explainable. As McCartney et al. reported, CTx agent can cause keratinization of the nasal mucosa presumably by affecting halting cell division 15) which is in several cases biopsy-proven fibrotic changes and marked keratinization at nasal mucosa by Esmaeli et al. and chronic inflammatory changes at lacrimal sac and sinus mucosa by John et al. 16) 18) Considering the fact that mucous edema in canaliculus and lacrimal sac by dacryoendoscope is characterized by CTx patients' endoscopic finding, it is more reasonable to think that the CTx agent can cause systemic inflammation, causing systemic edema. Also, it can be thought that CTx agents reduce the cycle of cell regeneration, causing keratinization and fibrotic changes in nasolacrimal duct and inferior turbinate, which is lower part of lacrimal pathway, resulting in mucosal edema of the upper lacrimal pathway.

Mean onset after RAI was considered as delayed reaction(52.6±36.5 month). Morgenstern et al. described to explain the relation between RAI and NLDO due to the expression of a sodium iodine symporter system, which promotes iodide uptake, in the lacrimal sac and the nasolacrimal duct. Active iodine uptake mediated by NIS could be responsible for damage to the nasolacrimal duct. 17) This could explain a mechanism that iodine slowly accumulated in lacrimal sac and cause a delayed reaction. It is corresponding result with the dacryoendoscopic finding, the most obstructed area was lacrimal sac in RAI group, followed by canaliculus, nasolacrimal duct, and inferior turbinate. According to Shelpler et al 12), where there was uptake at lacrimal sac by thyrogen scan after Iodine treatment, biopsy results showed foreign-body reaction and fibrosis with no malignant cells, Iodine is thought to remain in lacrimal sac after Iodine treatment and cause inflammation as compatible as granulation finding in dacryoendoscope.

For both groups, the NLDO might be a minor problem because they are getting through life-threatening treatment and underwent treatments that could affect their whole body. Also NLDO secondary to CTx and RAI is a newly recognized complication, which is not very well known to majority of patients. But, physician who manage patient proceeding CTx and RAI should be aware of this complication and send patient to ophthalmologist early for surgical intervention could improve the quality of life of patients and sparing harder and larger surgery such as DCR.

There were several limitations to this study. First, the mean cumulative dose of systemic chemotherapy and radioactive iodine received was uncertain. Further studies are needed to establish the relationship

between cumulative dose and endoscopic treatment.

Second, the clinical findings inside the LDS were categorized according to the type and level of the obstruction only prior to treatment. Therefore, additional study on the followup findings of the LDS after silicone tube removal will further clarify our present findings as they relate to pathogenesis. In this study, we were able to identify dacryoendoscopic findings predicting surgical outcomes.

In conclusion, the dacryoendoscope has the advantage of being able to check in real time with the eyes and check the lesions that cause the LDO. Therefore, with dacryoendoscope, we are better able to understand the pathogenesis of PANDO for more accurate diagnosis and customized treatment of patients. MESI can be a good treatment of choice for patients undergoing CTx and RAI.

Declarations

Due to technical limitations, Declaration section is not available for this version.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

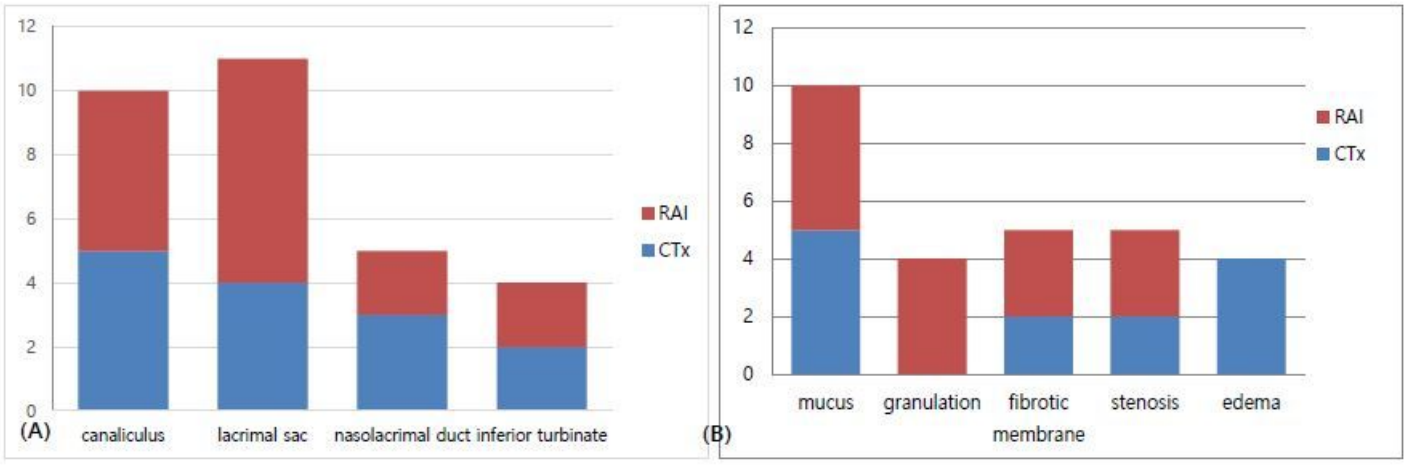
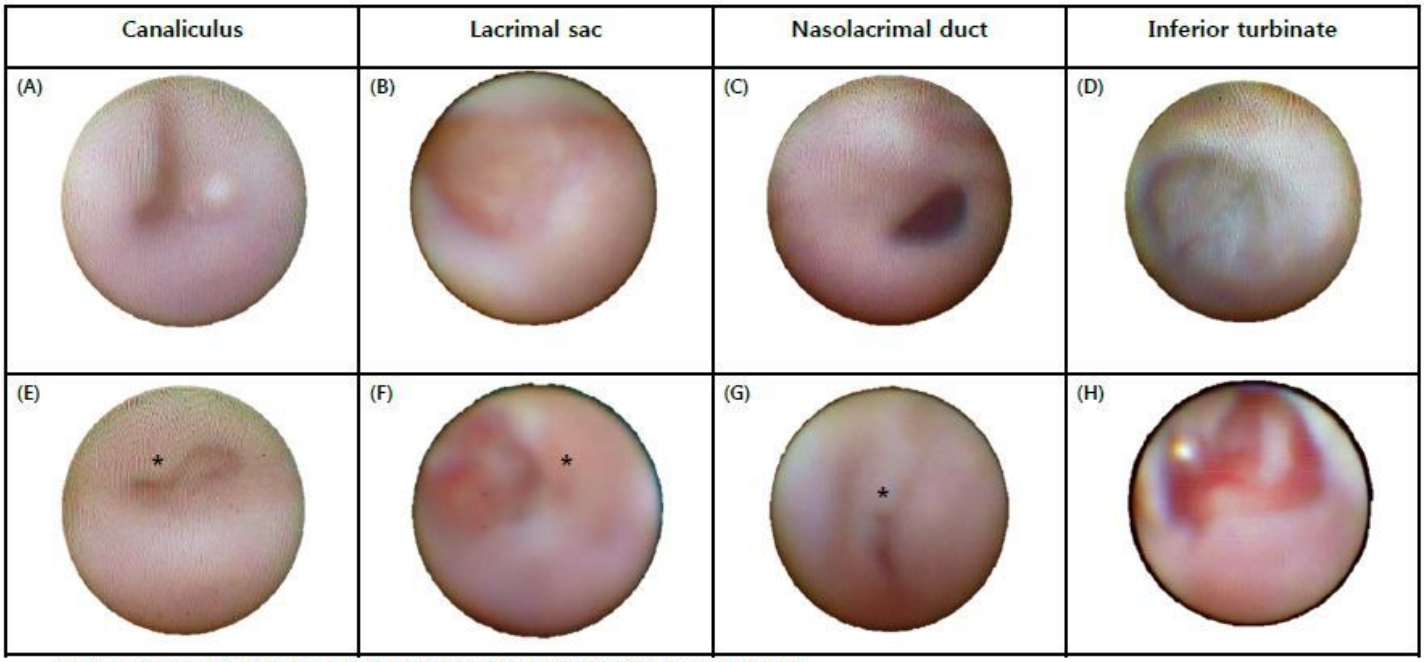


Figure 1

(A) D acryo endoscopic findings according to level of obstruction between CTx and RAI patients (B) D acryo endoscopic findings between CTx and RAI patients



(A) Mucosal edema after CTx(Docetaxel, Carboplatin, Trastuzumab, Pertuzumab) in the canaliculus (Case 2)
(B) Mucosal edema after CTx(Pemetrexed, Carboplatin) in the lacrimal sac (Case 5)
(C) Mucosal edema after CTx(Docetaxel, Carboplatin, Trastuzumab, Pertuzumab) in the nasolacrimal duct (Case 2)
(D) Membranous stenosis after CTx(Ifostamide, Methotrexate, Etoposide) in the inferior turbinate (Case 8)
(E) Mucosal granulation(asterisk) after RFA in the canaliculus (Case 16)
(F) Mucosal granulation(asterisk) after RFA in the lacrimal sac (Case 13)
(G) Mucosal granulation(asterisk) after RFA in the nasolacrimal duct (Case 12)
(H) Mucosal edema after RFA in the the inferior turbinate (Case 12)

Figure 2

Dacryoendoscopic findings after CTx and RAI treatment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.pdf
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