Sclerosing canaliculitis after 5-fluorouracil breast cancer chemotherapy

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CLINICAL STUDY

Abstract

Background **5-Fluorouracil is a pyrimidine analogue that inhibits DNA synthesis and is commonly used in the treatment of carcinomas of the breast, gastrointestinal tract and genitourinary tract. Excessive tearing that resolves on cessation of treatment is commonly described as a side effect of the drug. Permanent stenosis of the punctum and canaliculus is extremely rare, with only 12 cases reported in the world literature. We present three cases of established lacrimal outflow obstruction in patients who were treated with CMF (cyclophosphamide, methotrexate, 5-fluorouracil), a widely used regimen for metastatic breast cancer.**
Patient 1 **had right distal stenosis of her lower canaliculus and was syringed patent during dacryocystography with resolution of epiphora.**
Patient 2 **had proximal blockage of all canaliculi and underwent bilateral canaliculo-dacryocystorhinostomy with silicone tubes that temporarily relieved symptoms until tube removal. The proximal canalicular blockage recurred due to underlying extensive fibrosis.**
Patient 3 **had right proximal common canalicular stenosis and left distal canalicular blocks but declined surgery.**
Conclusion **With the rise in the incidence of breast carcinoma it is important that the attention of both ophthalmologists and oncologists should be drawn to the potential ocular toxicity of systemic 5-fluorouracil chemotherapy, which may lead to lacrimal canalicular fibrosis with permanent epiphora. The management of these patients is challenging as there is a continuous spectrum of canalicular involvement from focal to diffuse; therefore early referral is recommended. Moreover as no consensus has been reached as how best to manage this unique small group of patients, we review the literature and discuss the implications for treatment.**

Key words Epiphora, 5-Fluorouracil, Sclerosing canaliculitis

5-Fluorouracil (5FU) is a principal chemotherapeutic agent used solely or in combination with other cytotoxics in adjunctive treatment of metastatic breast, gastrointestinal and genitourinary carcinomas.[1] It is a pyrimidine analogue that leads to premature chain termination in the synthesis of double-stranded DNA.

Excessive lacrimation associated with the use of systemic 5FU is well documented in the literature as a result of high concentrations of the drug secreted in the tear film, and tends to resolve after therapy has been terminated. Permanent stenosis of the lacrimal tract is uncommon and there have been few reports detailing management.[2–4] In this series we present three cases of canalicular stenosis after systemic treatment with 5FU in combination chemotherapy with cyclophosphamide and methotrexate (CMF). This is a commonly used regime for metastatic breast carcinoma.[5] In the context of the management of a life-threatening disseminated malignancy, the possibility of leaving a patient with bilateral epiphora after chemotherapy may not be a major consideration in the choice of treatment; however, there may be significant impairment of quality of life. With the increasing rates of breast carcinoma in the UK it is important that ophthalmologists are aware that the underlying cause of epiphora with canalicular disease may be due to systemic treatment with 5FU. The management of these cases is challenging as there is a spectrum of stenosis from focal to diffuse.

Patients (Fig. 1, Table 1)

Case 1

A 53-year-old woman was referred to the Adnexal Clinic in May 1995 with a 4 month history of bilateral epiphora. This had commenced during the second cycle of chemotherapy and had persisted for 5 months (1 month before the termination of chemotherapy) before she was referred to the Adnexal Clinic. Initially both eyes had felt very dry and sore then subsequently they became very watery, worse when the patient was outdoors, causing inability to drive on some days.

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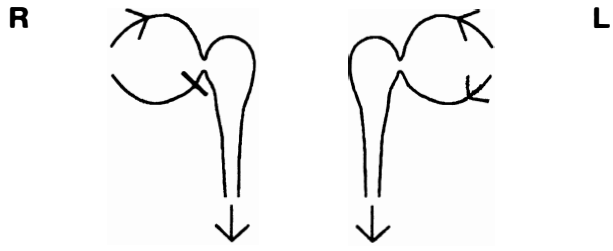
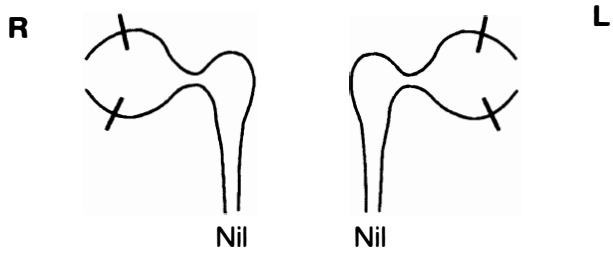
Case 1



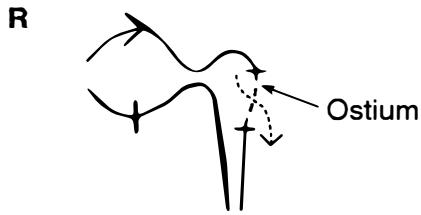
Right distal lower canalicular block - separate entry of upper and lower canaliculi into lacrimal sac – upper canaliculus patent.
Left patent via both upper and lower canaliculus.

Case 2 a) Preoperative



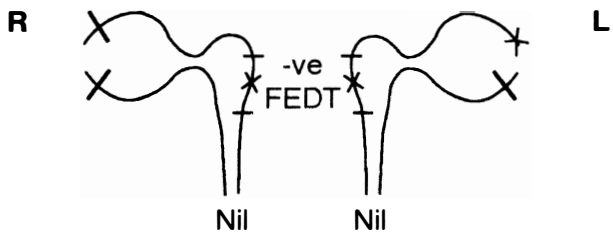
Bilateral proximal upper and lower canalicular block. (4mm patent)

b) Post-CDCR – immediately after silicone tube removal



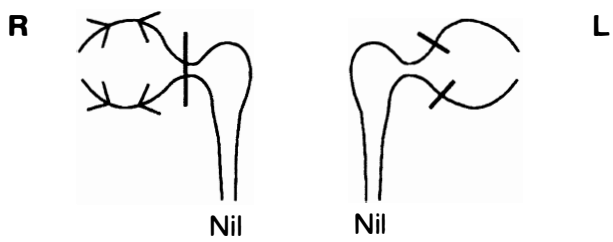
Right patent via upper canaliculus. Lower canaliculus block. (6mm proximal patent)

c) Four months after removal of tube



Bilateral proximal canalicular block 2mm patent apart from left upper canaliculus, completely occluded

Case 3



Right proximal canalicular block – left upper and lower mid-canalicular block

Fig. 1. *Line drawings of the three cases of canalicular blockage, based on clinical syringings and nasal endoscopy. CDCR, canaliculo-dacryocystorhinostomy; FEDT, functional endoscopic dye test.*

Table 1. *Review of our new cases of lacrimal tract obstruction*

Age (yr)/Sex	Tumour	Regimen	Onset (months)	Type of lacrimal block	Treatment
53/F	Breast	CMF (dose as stated in paper)	3	Right distal lower canalicular block	Probed patent during DCG
48/F	Breast	CMF (dose as stated in paper)	3	Bilateral proximal upper and lower canalicular block	Failed bilateral canaliculo-DCR + silicone tubes; conjuctivo-DCR + Pyrex tubes planned
68/F	Breast	CMF (dose as stated in paper)	1	Proximal common canalicular block OD; mid upper and lower canalicular block OS	Declined treatment

DCG, dacryocystogram; DCR, dacryocystorhinostomy.

She had undergone a right mastectomy in October 1994 with axillary clearance. Histological examination showed a 4 cm invasive lobular carcinoma grade II with positive nodes (8/12). She was commenced on tamoxifen 20 mg o.d. then had six, monthly cycles of CMF, consisting of methotrexate and 5FU intravenously on days 1 and 8, and cyclophosphamide 150 mg orally from days 1 to 14. She also had radiotherapy to the chest wall using tangential fields delivering a pre-set dose of 4000 cGy in 15 fractions.

There was no history of facial trauma, allergy, conjunctivitis, ocular herpes simplex or use of topical ocular medication. On syringing, the right lower canaliculus was patent up to 7 mm with either a distal block of a short segment of the lower canaliculus or a proximal block of the common canaliculus, depending on the anatomical configuration of the canaliculi. The upper punctum and canaliculi were patent throughout. The patient then underwent a dacryocystogram during which the short segment of stenosis was overcome with vigorous probing (see Fig. 2 showing the dacryocystogram following probing). She has remained asymptomatic throughout 24 months of follow-up.

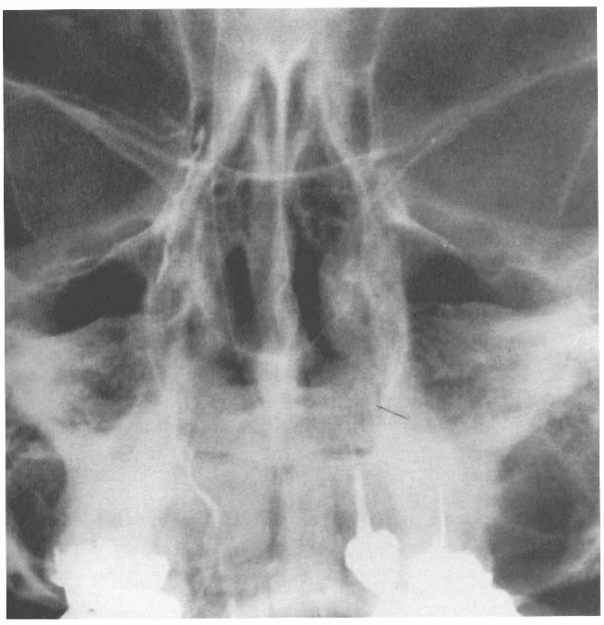


Fig. 2. *Case 1. Right dacryocystogram demonstrating the previously stenosed distal portion of the right lower canaliculus syringed patent.*

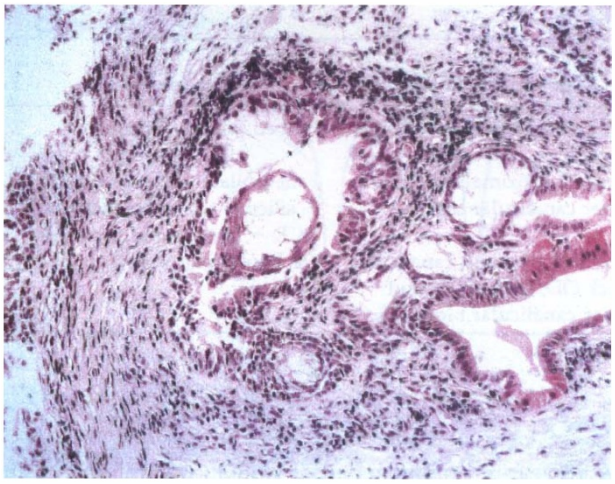
Case 2

A 48-year-old premenopausal woman was referred with an 18 month history of bilateral epiphora. She was diagnosed with breast carcinoma in May 1994, and underwent a lumpectomy with axillary clearance for a T2 ductal carcinoma with 2/7 positive nodes and five monthly cycles of CMF chemotherapy but no tamoxifen followed by radiotherapy.

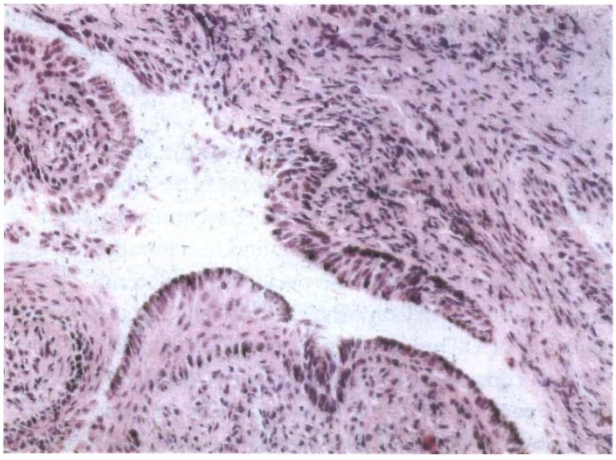
Severe epiphora commenced 3 months after chemotherapy was initiated. There was no other relevant history. Clinically there were short sections of patent proximal upper and lower canaliculi bilaterally (approximately 4 mm). She underwent bilateral canaliculo-dacryocystinorhinostomy in August 1996 with insertion of O'Donoghue silicone tubes, as she did not want to consider a conjunctivo-dacryocystorhinostomy with a permanent Pyrex glass tube. On retrograde intubation at surgery, blockage of the common canaliculus was confirmed and the section of the common canaliculus with obvious fibrous adhesions was excised. O'Donoghue tubes were introduced with some force. The extensive fibrous adhesions found blocking the canaliculi and the fibrotic lacrimal sac were sent for histopathological examination. This showed intraluminal and pericanalicular fibrosis with (Fig. 3) chronic inflammatory infiltrate and some intra-epithelial iron.

Her recovery was complicated by granuloma formation at the right upper punctum 2 months post-operatively, which responded to a single topical application of a silver nitrate stick. She received topical steroid treatment and the silicone tubes were left in for 4 months. Endonasal endoscopic examination whilst the tubes were *in situ* revealed tight mucosa around the site of exit of the tubes from the ostium on the lateral nasal wall. No movement of the tubes was detected on blinking, and there was a negative functional endoscopic dye test (visual Jones 1 test) when the tubes were *in situ*, suggesting deeper fibrosis causing poor lacrimal pump function.

Immediately following removal of the tubes the right inferior canaliculus was patent for 6 mm from the punctum and the upper canaliculus was patent to probing and syringing allowing free flow into the lacrimal system. However, when the patient was reviewed 4 months after tube removal she again complained of epiphora. Probing on the right side



(a)



(b)

Fig. 3. *Case 2. (a) H&E-stained specimen demonstrating fibrosis with chronic inflammatory infiltrate. (b) Iron stain of specimen showing some intra-epithelial iron deposition.*

revealed only short patent sections (approximately 2 mm of upper and lower canaliculi); on the left the upper canaliculus was entirely blocked and there was only a short segment (approximately 2 mm) of patent lower canaliculus. Endoscopically the nasal mucosal ostia were closed and non-functional. Insertion of permanent Lester Jones (Pyrex) tubes is planned.

Case 3

A 68-year-old woman was referred in December 1994 with a 3 year history of bilateral epiphora. She had undergone CMF chemotherapy for her breast carcinoma in the USA with 4 weekly intravenous treatment that was tailored to response. Constant epiphora started 1 month after commencement of treatment. She had consulted a local ophthalmologist in her country who reassured her that the epiphora would resolve spontaneously. There was no other relevant history. On clinical examination she had right proximal common canalicular block and left upper and lower canalicular block.

Dacryocystography showed left distal common canalicular block (Fig. 4). The patient was offered surgery but declined.

Discussion

The three patients in our series illustrate the range of sclerosing canaliculitis following breast cancer treatment with CMF, ranging from focal stenosis to widespread occlusion. Most ophthalmologists are familiar with the use of antimetabolites in glaucoma surgery, but may be unaware that for many years there has been widespread use of 5FU in large doses systemically for metastatic carcinoma of the breast and bowel. In early breast cancer all clinically apparent disease may be removed surgically and after surgery various types of systemic adjuvant therapy can be considered. Of these, the two most accepted forms involve either tamoxifen, an anti-oestrogen often taken for life, or a combination of cytotoxic drugs. In Britain about 40% of patients with breast cancer are over 70 years, 40% are aged between 50 and 69 years and only 20% are under 50 years when diagnosed. Those undergoing polychemotherapy generally belong to a younger age group with node-positive disease, as tamoxifen is unsuitable for premenopausal women.

The individual contributions of each drug of the CMF regimen to the onset of canalicular fibrosis with secondary intractable epiphora is difficult to quantify as each drug has some ocular side effects, but the evidence based on previous literature points to 5FU toxicity being the main cause of epiphora.

Cyclophosphamide is an alkylating agent and ocular toxicity has been reported to manifest as blurred vision,[6] keratoconjunctivitis sicca,[7] blepharoconjunctivitis and pupillary abnormalities.[8] Stevens Johnson syndrome and cataract formation have been reported when cyclophosphamide has been used in conjunction with steroids.[9]

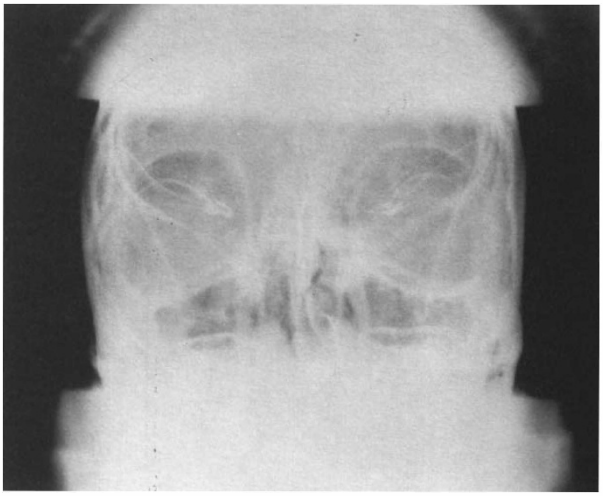


FIg. 4. *Case 3. Dacryocystogram showing right proximal common canalicular block and left distal common canalicular block.*

Methotrexate is a folic acid analogue and inhibits dihydrofolate reductase, which transforms folic acid into coenzymes essential for DNA synthesis. Ocular toxicity has been reported in one-quarter of all patients undergoing high-dose intravenous therapy (30–250 mg/kg) and includes periorbital oedema, epiphora, blepharitis, conjunctivitis and decreased reflex tear secretion.[10] Symptoms resolve rapidly, often within days after termination of treatment, and are ameliorated by the use of tear substitutes.[11] Tear levels of methotrexate reflect serum levels; there is, however, no correlation of ocular symptoms with tear concentration, and they are felt more likely to be related to its anti-mitotic effect. Methotrexate has been shown to reduce reflex tear production.[11] We are unaware of any evidence that methotrexate causes canalicular disease.

5FU is a pyrimidine analogue that is a potent inhibitor of thymidylate synthetase and hence blocks effective DNA synthesis. Systemic administration has most effect on organ systems that have a rapid turnover of cells, including the gastrointestinal tract, bone marrow and the ocular surface epithelium. 5FU has been shown to inhibit the mitosis of retinal pigment epithelial cells and fibrocytes *in vivo* and *in vitro*,[12] and topical use also impairs corneal and conjunctival re-epithelialisation[13] – hence its local use in augmented trabeculectomies, and increasing use in oculoplastic procedures where excessive scarring reaction is anticipated. For systemic use in oncology, it is generally administered by rapid intravenous injection with a plasma half-life of 10 min. Ocular side effects from systemic treatment manifest as either ocular surface and/or neuromotility disorders including blurred vision, ocular pain, photophobia, accommodation disorders, oculomotility disorders, nystagmus, keratoconjunctivitis, optic neuropathy, periorbital swelling and pain, cicatricial ectropion,[14] epiphora, and dacryofibrosis, chronic canaliculitis and stenosis.[9]

All our patients developed epiphora within months of commencing CMF chemotherapy and this reflects the time course in the literature (Table 2). Complaints of epiphora in patients treated with systemic 5FU were first described in a variety of correspondence in oncology journals, notably Hammersley *et al.*[15] in 1973 who noted that 14 patients receiving 5FU developed epiphora that resolved completely within a fortnight of cessation of the chemotherapy with no permanent anatomical alterations to the lacrimal drainage system. Christophidis *et al.*[16] measured the concentration of 5FU in tears and plasma 15 min after its intravenous administration and showed

Table 2. *Literature review of lacrimal tract obstruction attributed to 5FU*

Author	Age (yr)/Sex	Tumour	Regimen	Onset (months)	Type of lacrimal block	Treatment
Caravella *et al.*[1] (1981)	54/F	Recto-sigmoid	5FU (600 mg i.v. for 5/7 then 500–800 mg weekly)	4	Stenosed puncta with mucosal membrane, slight stenosis of lower canaliculus OS	Free drainage into lacrimal system on syringing
	58/M	Colon	5FU (800 mg i.v. for 5/7 then 500–1100 mg weekly)	2.5	Three stenotic puncta, inferior puncta OD totally occluded by membrane. Inferior canaliculus OD uniform stenosis	Bilateral free irrigation
	38/M	Small bowel	5FU (500 mg i.v. for 5/7 then 500–750 mg weekly)	4	Four severely stenosed puncta, severe uniform stenoses of all canaliculi	Probed patent, silastic tubes inserted; recurred when removed tubes reinserted
	43/F	Breast	CMF (dose as stated in paper)	'Shortly'	Stenotic lower lid pinctum OD	No treatment
Seiff *et al.*[3] (1985)	69/F	Pancreas	5FU (12.5 mg/kg loading dose for 5/7 then 500 mg i.v. weekly)	26	Impossible to cannulate due to complete punctal and canalicular obsruction	Bilateral conjunctivo-DCRs (successful in relieving symptoms)
Brink and Beex[4] (1995)	58/F	Breast	5FU, tamoxifen	Immediate	Complete occlusion of all puncta by membrane	Membrane excised, topical steroids and antibiotics; conjunctivo-DCR declined
	62/F	Breast	CMF	Immediate	Four stenosed puncta, partial stenosis of lower canaliculi	Repeated probing, topical steroids; symptoms resolved on stopping 5FU
	49/F	Breast	5FU, tamoxifen	2	Severe stenosis of all puncta	Topical steroids; symptoms resolved on stopping 5FU
	70/F	Breast	5FU, tamoxifen	1	Punctal stenosis with occlusive membrane, bilateral lower canaliculi obstruction	Probed through occlusive membrane, artificial tears, resolution of symptoms
	70/F	Breast	5FU, tamoxifen	1	Complete lower punctal stenosis OS, complete canalicular obstruction OD	Conjunctivo-DCR OD

that secretion of the drug into the tear film was idiosyncratic and only present in the patients complaining of epiphora; the concentration in the tears was comparable to plasma levels of the drug.[16] This strongly suggests a positive link between tear film levels of 5FU and symptoms of epiphora. Caravella *et al*.[2] were the first to describe an anatomical disturbance of the lacrimal drainage system in a series of four patients in 1981. This was followed by subsequent reports in a variety of patients undergoing chemotherapy for breast or gastrointestinal malignancies with 5FU as the sole cytotoxic agent or in conjunction with other antimetabolites.[3,4]

It is important to differentiate the effects of topical application versus parenteral 5FU. Topical applications only exposes the ocular surface transiently to high levels of the drug, which is rapidly washed away by perfusion of normal saline, only minimal amounts entering the lacrimal system. The doses used peri-operatively and post-operatively as topical and subconjunctival injections in ophthalmology are in the region of 10 mg in 0.2 ml. The systemic doses recommended by Aisner *et al*.[17] are six courses of a 4 week cycle with cyclophosphamide 100 mg/m^2 p.o. days 1 to 14, together with methotrexate 40 mg/m^2 i.v. and 5FU 600 mg/m^2 i.v. on days 1 and 8.

The aetiology of ocular surface toxicities from systemic 5FU is often multifactorial. Systemic high doses of 5FU may produce lacrimal gland toxicity, causing hypersecretion with resulting higher levels of the drug in the tears. 5FU-induced cicatricial ectropion and dacryostenosis further exacerbate ocular toxicity. The development of permanent dacryostenosis represents the end stage of a cicatricial process that may be arrested if recognised; 5FU may be stopped and lid massage and topical corticosteroids initiated. There is no conclusive evidence that topical steroids inhibit fibrosis.[4] If the drug cannot be stopped, prophylactic silicone intubation of the lacrimal system has been advocated.[4] Permanent lid and lacrimal system abnormalities may necessitate surgery with an uncertain prognosis. The histological examination of the biopsy of the distal canaliculus and lacrimal sac taken at surgery (25 months after the onset of epiphora) confirmed a chronic inflammation and pericanalicular fibrosis, consistent with the clinical findings. Although this does not specify the aetiology, it confirms the inflammatory component, which may be important in the management of the acute stage and prevention of subsequent pericanalicular and sac fibrosis.

We would like to consider the two components of lacrimal drainage affected in our cases: the physiological and the anatomical role of the canaliculi in lacrimal drainage.

In the physiological lacrimal pump mechanisms described by Jones[18] and Becker[19] the canaliculi are sandwiched between the superficial and the deep (tensor tarsi) fibres of the orbicularis. The positioning of these fibres is crucial to effective lacrimal drainage and is invariably affected in any cicatricial process involving the surrounding tissues. This is especially significant after dacryocystorhinostomy (DCR), when we observed very poor movement of the nasal mucosal ostium in case 2. This is most likely due to the element of pericanalicular obstruction with scarring of the walls of the canaliculi and sac. It is interesting to note that no 'lacrimal diaphragm' (nasal mucosa spanning the osteotomy) movement was visualised endoscopically with tubes *in situ*. Normally, tubes are seen moving medially on eyelid closure and laterally on eyelid opening, corresponding to the movement of the lacrimal diaphragm moving in the opposite direction. On the basis of our endoscopic experience we regard lack of tube movement as a poor prognostic sign for lacrimal function after tube removal. In this case we feel that even had the anatomical drainage remained patent the actual symptoms of epiphora were unlikely to have been abolished.

Anatomically, even small amounts of canalicular obstruction can cause epiphora. The pathology of the canalicular obstruction has been divided into suppurative and non-suppurative.[20] The pathology induced by systemic chemotherapeutic agents falls into the latter group. 5FU inhibits cells only in the active mitotic phase, which are prevalent in epithelial surfaces. High concentration in lacrimal secretions causes inflammation of the lining of the canaliculi (intracanalicular obstruction) similar to the pathology in herpes infections and drug-induced cases (e.g. phospholine iodide[21] and adrenaline[22]).

Treatment of non-suppurative canalicular obstruction depends on the site of blockage. Careful clinical assessment often combined with imaging is recommended. Distal membranous common canalicular obstruction requires a DCR, removal of the occluding membrane and temporary silicone intubation for approximately 8–12 weeks. Proximal common canalicular obstruction usually requires a canaliculo-DCR with a longer period of intubation. Distal obstruction of the canaliculi (more than 8 mm remaining patent) can be treated with the excision of the scar tissue and the occluded canaliculus followed by anastomosing the remaining patent canaliculi to the lacrimal sac with the formation of DCR flaps in the normal fashion in a canaliculo-DCR. Transcanalicular YAG laser[23] followed by silicone intubation or balloon catheter dilatation has also been recommended for canalicular obstruction with varying degrees of success dependent on the extent of the occlusion. Treatment of proximal canalicular obstruction is classically a conjunctivo-DCR and the placement of a permanent Lester Jones (Pyrex) tube.

The management of our cases is challenging due to the continuous spectrum of stenosis ranging from focal to diffuse. Case 1 had a distal lower canalicular stenosis overcome by dilation. Transcanalicular YAG laser could have been beneficial here with or without intubation, as the distal lacrimal excretory system was patent. Case 2 wanted to avoid a conjunctivo-DCR even though at pre-operative assessment there was less than 8 mm of patent canaliculi. We decided to try canaliculo-DCR with silicone tubes as there was a small chance of success and

this would avoid a permanent Pyrex glass tube and all the long-term management problems associated with it. It was not possible to predict pre-operatively the extent of the occlusion distal to the point where it was detected and the occlusion could have been patchy. At surgery occlusion was obviously extensive but we nevertheless proceeded with a canaliculo-DCR. The patient still complained of epiphora with the silicone tubes *in situ* and endoscopically no fluorescein was seen draining around the tubes even 3 min after the instillation of g. fluorescein 2% into the conjunctival fornix (a negative functional endoscopic dye/visual Jones 1 test). In addition, there was no detectable movement, on repeated blinking, of the lateral nasal wall mucosa in the region of the bony ostium (the 'lacrimal diaphragm'). It is interesting to note that the patient was partially symptom free for a short period following removal of the silicone tubes before recurrence of subjective epiphora. However, the performance of canaliculo-DCR was not entirely in vain as it will facilitate the easy placement of a Lester Jones tube, there now being a reasonable osteotomy filled with fibrous tissue only. Case 3 represented proximal common canalicular occlusion that is likely to have responded well to canaliculo-DCR with silicone tubes or conjunctival-DCR with Lester Jones tube.

The variability in the clinical picture is reflected in the literature, as the differing degrees of pericanalicular fibrosis make a unifying approach extremely difficult. We recommend that each case should undergo thorough assessment by a lacrimal ophthalmic surgeon. It is difficult to predict the subgroup of patients at risk of developing permanent lacrimal abnormalities. Oncologists should be aware that lacrimal assessment and management are available, but that the management can sometimes be difficult if there is pericanalicular disease.

The use of polychemotherapy produces host systemic toxicity greater than expected using a single agent. The effect on the eye is not well documented. All our patients developed epiphora concurrent with the commencement of chemotherapy with no prior history or predisposing factors to lacrimal obstruction. The debility caused by bilateral epiphora may be significant; therefore it is paramount that clinicians treating these patients accurately enquire, and document eye problems with appropriate referral for a complete eye and lacrimal assessment. Early detection and management may prevent the later fibrotic sequelae and risk of permanent epiphora. Given the improving survival of cancer patients and the rise in the incidence of breast carcinoma, the next decade may see an opening of the floodgates of the long-term sequelae of cytotoxic chemotherapy.

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